JUL 28 1939
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VOL. I. No. 3 JULY, 1939

BRITISH HEART JOURNAL

FOR THE STUDY OF
CARDIOLOGY AND THE CIRCULATION

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APPOINTED BY
THE CARDIAC SOCIETY OF GREAT BRITAIN AND IRELAND

LONDON
BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, W.C.1

PUBLISHED QUARTERLY SUBSCRIPTION 25/- PER ANNUM

CONTENTS

PAGE

Alcoholic Beri-beri Heart
By A. Morgan Jones and Crighton Bramwell 187

The Drug Treatment of Hyperpiesia
By William Evans and Owen Loughnan 199

Electrocardiograph Electrolytes
By G. H. Bell, J. A. C. Knox, and A. J. Small 229

Sir James Mackenzie's Heart . . . By David Waterston 237

Cardiac Myxoma: A Clinical and Pathological Study
By R. E. M. Fawcett and E. Milford Ward 249

Standardization of Methods of Measuring the Arterial Blood Pressure
A Joint Report of the Committees Appointed by the Cardiac Society of Great Britain and Ireland and the American Heart Association. 261

ALCOHOLIC BERI-BERI HEART

BY

A. MORGAN JONES AND CRIGHTON BRAMWELL

From the Cardiographic Department, Manchester Royal Infirmary

Received February 12, 1939

Heart failure due to vitamin deficiency has not hitherto attracted much attention in this country. A single case was reported recently by Price (1938) and another by Yudkin (1938). The case that follows illustrates certain features characteristic of the condition.

CASE REPORT

A man, aged 36, was admitted to the Manchester Royal Infirmary on November 11, 1938, with acute heart failure. The distribution of the œdema was unusual and, in certain respects, resembled that of renal rather than that of cardiac insufficiency. The face was puffy, the eyelids swollen ; there was massive œdema of the legs extending to the thighs ; the penis and scrotum were enormously swollen ; the abdomen was distended and contained free fluid ; moist sounds were present in the lungs ; there was slight engorgement of the veins of the neck and the liver was palpable.

Swelling of the ankles, which was greatest in the morning and diminished towards evening, had first been noticed only two weeks previously, and shortness of breath on exertion had been present for only ten days. Three months prior to admission the patient had felt perfectly fit, but his friends had remarked on the fact that he had required to pass water surprisingly seldom, considering the large quantities of beer he drank. The other prominent symptoms were anorexia and epigastric pain. These will be referred to later.

On examination of the circulatory system, the heart was found to be greatly enlarged (Fig. 1), the maximal cardiac impulse being situated in the fifth space 4 cm. beyond the mid-clavicular line. On auscultation, there was typical presystolic gallop rhythm with a loud apical systolic murmur. The resting pulse rate was 120 and the rhythm regular. The blood pressure was 160/90 mm. ; but the diastolic endpoint was poorly defined, the sounds gradually diminishing in intensity and a systolic bruit being heard down to a decompressing pressure of 30 mm.

The knee-jerks could be elicited only on reinforcement and the ankle-jerks were absent. There was no sensory loss to pain, light touch, vibration sense,

or sense of passive movement and position. The urine was acid, with a specific gravity of 1010 : repeated tests failed to show any albumin.

FIG. 1.—Teleradiogram, Nov. 18.

Apart from influenza in 1930, with which he was off work for only one week, there was no previous medical history of significance. He had never suffered from rheumatic fever, sore throats, chorea, scarlet fever, diphtheria, or bronchitis.

Diagnosis.—The clinical picture was atypical. The association of gallop rhythm with extensive œdema, the unusual distribution of the œdema, the

rapidity with which it had appeared and the fact that, until recently, the patient had been a perfectly healthy man suggested that heart failure, in this case, was not due to any of the usual causes.

In searching for an ætiological factor, the possibility of a vitamin deficiency occurred to us. Further enquiry into the history revealed the fact that for seventeen years, during which time he had been employed as a navvy, he had taken 7 to 8 pints of beer daily.

Eighteen months prior to admission he had become a bar attendant, and since then had taken between 14 and 18 pints of beer every day. He had gradually lost appetite and for the greater part of this period had never had more than one meal a day, and had often gone a whole week without eating any solid food. For six weeks he had vomited after every meal.

Cases of beri-beri, such as occur in the East, are rarely seen in Britain ; but a similar clinical picture may be produced by chronic alcoholism, which many workers consider to be a potent factor in inducing dietary deficiency. It leads to anorexia and so to a deficient food intake ; and, since beer is deficient in vitamin B_1 (Donovan and Hanke, 1936), the diet becomes deficient in this vitamin content although its caloric value may be adequate, when little other food is taken. Cowgill (1934) has pointed out that one of the first signs of vitamin B_1 deficiency is anorexia, which in turn leads to further diminution in vitamin intake. Thus a vicious circle is set up. Alcohol can supply a high caloric value with a very low vitamin content. This is the ideal combination for the development of beri-beri, for the higher the caloric intake the greater is the requirement of vitamin B_1.

It is interesting to note that the similarity in distribution of the œdema in cases of chronic alcoholism and " beri-beri heart " should have attracted attention before the connecting link between the two conditions was recognized. Writing in 1906, before vitamins had been discovered, Graham Steell referred to the subject in these words :

> " Capricious distribution of dropsy is specially apt to occur in cases of the cardiac muscle-failure of beer-drinkers and of the disease known as beri-beri, of both of which diseases, it is curious to note, peripheral neuritis is a clinical feature. . . . Curious special localizations of œdema met with, in cases of the kind, have been the scrotum, and together the upper trunk, upper extremities, and scalp and neck, so that the œdema simulates that resulting from mediastinal tumour."

Laboratory Investigations.—Electrocardiograms (Fig. 2) showed no significant abnormality. On the third day the T wave in lead III was upright, on the fourteenth day it was almost isoelectric, and a month after admission it was inverted. A similar change was noted by Keefer (1930) in two cases, but it is doubtful whether it is of any significance.

The plasma proteins were not estimated during the acute stage, but ten days after admission the albumin : globulin ratio was 5·5 : 2·0, and a subsequent determination about seven weeks later gave the ratio 5·5 : 2·1. On the third day the blood urea was 20 mg. per 100 cc. and the urea clearance test 67 per

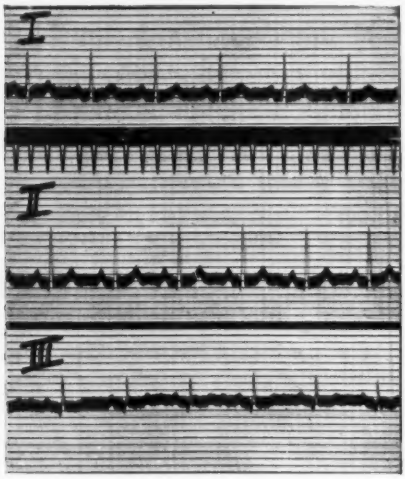

FIG. 2.—Electrocardiogram, Nov. 14. Time intervals, 0·2 sec. Calibration 2 cm.=3mv. A month later T was inverted in lead III.

cent. of the average normal value. A fractional gastric analysis on the fourth day gave a normal result. A blood count on the third day showed :

Red blood corpuscles	4,960,000 per c.mm.
Hæmoglobin	96 per cent.
Colour index	0·97
White blood corpuscles	4,200 per c.mm.
Polymorphs	53·5 per cent.
Lymphocytes	35·5 per cent.
Large mononuclears	7·0 per cent.
Eosinophils	3·5 per cent.
Basophils	0·5 per cent.

A subsequent count, about seven weeks later, showed slightly higher figures for the red cells and hæmoglobin and the white cells had risen to 6000 with 57 per cent. polymorphonuclears, 35 per cent. lymphocytes, and 3 per cent. eosinophils.

Treatment.—The patient was kept in bed and given daily intramuscular injections of 2 mg. of vitamin B_1, in the form of Benerva (Roche) ; the total quantity given during the seventeen days he was in hospital being 30 mg. Apart from a full diet and Easton's syrup, he received no other treatment.

Progress.—For one day the patient refused all food, but then regained his appetite and ate well. During the first day he passed only 16 ounces of urine ; but about twenty-four hours after the first injection of vitamin B_1, a brisk diuresis set in, and in the next three days he passed 196 ounces. His weight on admission was 155 lb. ; four days later it was 146 lb.—a loss of 9 lb. On

admission his pulse rate was 120 ; on the third day it varied between 80 and 90, and a week later had reached a fairly steady level of 60 to 70. These values are recorded graphically in Fig. 3. On the fourth day he felt perfectly

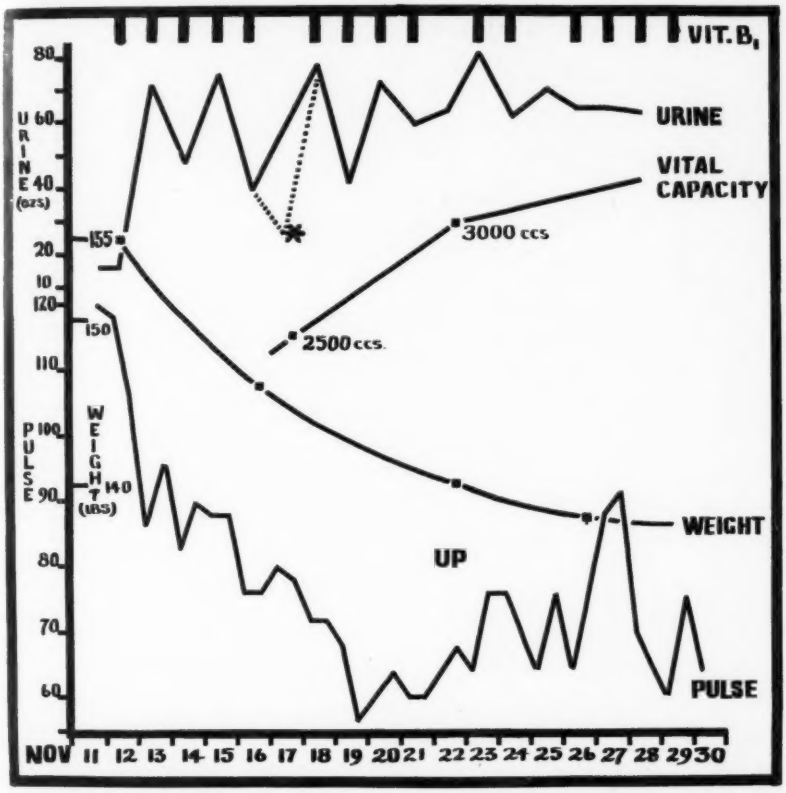

FIG. 3.—Pulse rate, weight, vital capacity, output of urine and dosage of vitamin B_1. Each mark at the top of the figure indicates a dose of 2 mg. vitamin B_1 given intramuscularly. * The whole of the urine was not measured on this date. The vital capacity curve is exterpolated towards a reading taken shortly after the patient was discharged from hospital.

fit, his appetite was excellent, gallop rhythm was no longer present and the œdema had practically disappeared.

The vital capacity on the third day was 2500 c.c. (calculated normal 4175 c.c.) ; five days later it had risen to 3000 c.c. and three weeks after admission it was 3250 c.c. A teleradiogram taken three days after admission showed great cardiac enlargement and considerable pulmonary congestion. Four days later the appearances had altered very little (Fig. 1), but during the next ten days the heart diminished considerably in size (Fig. 4) and the pulmonary congestion completely disappeared.

Ten days after admission he was allowed up and seven days later he was discharged from hospital, since when he has remained fit.

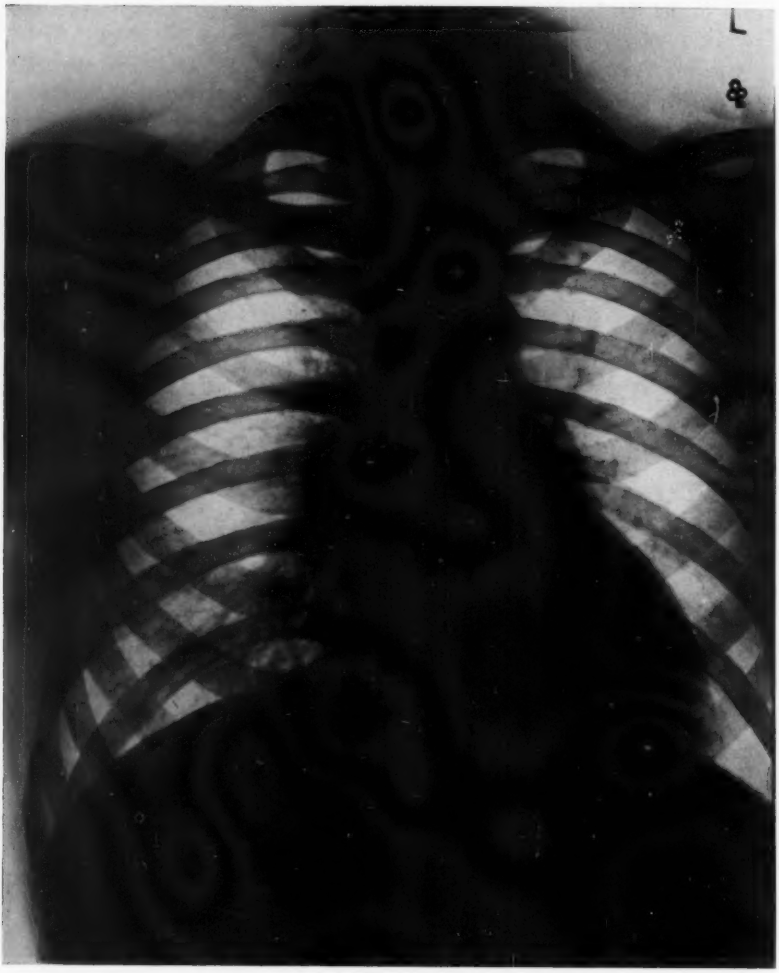

FIG. 4.—Teleradiogram, Nov. 29.

THE BERI-BERI HEART

The classical features of " beri-beri heart " as seen in Java were fully described by Aalsmeer and Wenckebach (1928) and later by Wenckebach (1932 and 1934). These workers emphasized the predominant element of right-sided heart failure without pulmonary congestion. Weiss and Wilkins (1936 and 1937*a*) published a series of 120 cases observed in America, many of which appeared to be attributable to chronic alcoholism. They recorded a large and varied list of signs and symptoms, and stated that the cardiovascular disturbances caused by nutritional deficiency did not form a single rigid clinical syndrome. They

pointed out the importance of dietary deficiency in precipitating cardiac failure in other forms of organic heart disease.

Hawes (1938) described the clinical picture of " shoshin " (the severe form of acute congestive failure due to beri-beri which is seen in the East) as that of a desperately ill patient, vomiting, breathless and restless, with severe epigastric pain, enlarged heart, dependent œdema, engorged veins, tachycardia, and a low diastolic pressure. This description is almost identical with that given by Aalsmeer and Wenckebach (1928) for what they called the " acute pernicious " beri-beri heart. They divided cardiovascular beri-beri into three groups—a mild ambulatory type with dyspnœa and palpitation ; a moderately severe type with cardiac enlargement, œdema and polyneuritis ; and the acute pernicious form described above.

Our case differs from the moderately severe type by the absence of polyneuritis, yet did not present so advanced a clinical picture as the acute pernicious type. It is very similar to the case described by Price (1938) and to one of those reported in detail by Weiss and Wilkins (1936), both of which were attributed to chronic alcoholism.

The absence of signs of polyneuritis is not uncommon in the more severe and acute forms of beri-beri heart, and Keefer (1930), who described 15 cases of beri-beri heart in Japan, showed that the patients who developed cardiac insufficiency were those with least involvement of the nervous system. He regarded this as due to the protection of the heart by the motor disability caused by the polyneuritis. If this hypothesis be correct, we should not expect to find severe signs of polyneuritis in the more acute forms of beri-beri heart, though Strauss (1938) believes that it is rare to find beri-beri heart without at least minimal signs of polyneuritis. Aalsmeer and Wenckebach (1928), on the other hand, think that cardiac enlargement may be detected long before the appearance of the first signs of polyneuritis. Birch and Harris (1934) state that the biochemical lesion caused by vitamin B_1 deficiency seems to affect the heart almost immediately and may cause sudden death from heart failure, while its toxic action on the central nervous system proceeds more slowly.

Allied Conditions

The biochemical mechanism underlying the production of alcoholic beri-beri heart is the subject of controversy, and, although deficiency of vitamin B_1 is of paramount importance, it is possible that this is not the only factor. Before concluding that œdema associated with dietary deficiency is due to lack of vitamin B, other abnormalities in the diet, such as deficiency of proteins or total calories, must be considered, especially when these deficiencies are associated with an increased fluid intake. Such types of deficiency, however, cannot explain the cardiovascular signs and symptoms which are seen in cases like that which we have described, while the plasma protein values reported by Weiss and Wilkins (1936 and 1937*a*), in cases of alcoholic beri-beri are not sufficiently low to account even for the œdema.

The history in our case naturally led us to speculate on the possible relation

of alcoholic beri-beri heart to the so-called beer-drinker's heart. This diagnosis is now rarely made ; in fact, the disease seems almost to have died out. This might be accounted for either by the reduced consumption of beer at the present day, or by the fact that beer-drinker's heart is nothing more nor less than hypertensive heart disease. This latter hypothesis receives support from the fact, pointed out by Weiss and Wilkins (1937*b*), that the disappearance of this disease is chronologically related to the introduction of sphygmomanometry and to the recognition of the importance of hypertension in the production of cardiac hypertrophy and heart failure.

Other forms of œdema associated with dietary deficiency are so-called famine œdema and war œdema. In recent years these conditions have been studied comparatively little ; but most workers believe that they are essentially different from beri-beri. Nixon (1920) regards polyuria, bradycardia and asthenia as the essential clinical features of famine œdema ; whereas the dyspnœa, tachycardia, cardiac dilatation and signs of heart failure found in association with vitamin B_1 deficiency are absent. In fact, the only clinical feature common to the two conditions is the œdema.

The nature of the dietary deficiency in these conditions has been studied by several workers. Maver (1920) has surveyed the whole field and gives a comprehensive bibliography. She does not believe that war œdema is due to a deficiency of one or more specific vitamins, but that it is the result of a protracted existence on a diet deficient in total calories and especially in protein, and that a high fluid intake and possibly a high salt intake are important accessory factors. She points out that a combination of low calories, low protein and excessive fluid intake will lead experimentally to a severe dropsy corresponding in all respects to war œdema. Cowgill (1934) failed to find any evidence of vitamin B_1 deficiency in diets under conditions where such œdema might be expected to occur.

The post-mortem appearances were studied by Porter in the Indian famine of 1877–78 (quoted by Nixon, 1920) and are those of starvation. He demonstrated the changes of brown atrophy in the heart ; this is unlike the post-mortem findings of Aalsmeer and Wenckebach (1928), and Weiss and Wilkins (1936 and 1937*a*) in beri-beri heart. These workers found hydropic degeneration and interstitial œdema of the cardiac muscle.

Thus it appears that these forms of œdema are ætiologically, clinically and pathologically distinct from the œdema associated with beri-beri heart.

Diagnosis of the Beri-Beri Heart

Severe cases of beri-beri heart are rare in this country ; yet their recognition is of importance, for they respond dramatically to specific treatment and very poorly to other measures.

The diagnosis rests essentially upon :

1. The dissimilarity of the clinical syndrome from that of heart failure due to other causes.

2. The absence of the more common ætiological factors responsible for producing heart failure.
3. The presence of a dietary abnormality compatible with a gross deficiency of vitamin B_1.
4. The response to treatment with vitamin B_1.

The diagnosis is corroborated by :

5. The presence of other signs and symptoms of vitamin deficiency.
6. Certain laboratory tests.

1. *The Clinical Syndrome.*—The distribution of the œdema is unusual. It may be most striking in the face and genitalia, and most pronounced in the morning, suggesting renal rather than cardiac insufficiency ; but the absence of albuminuria, the relatively high renal efficiency and the normal protein content of the plasma exclude this diagnosis. In our case there was less venous engorgement than one would expect in view of the extent of the œdema.

The association of gallop rhythm with extensive œdema is unusual in the other types of heart failure, but common in alcoholic beri-beri heart. Weiss and Wilkins (1936) discussed the clinical differences between beri-beri heart as seen in the East and in America, where it is usually due to chronic alcoholism. They emphasized the frequency of combined right and left heart failure in alcoholic beri-beri, whereas in the East right-sided failure is the rule (Aalsmeer and Wenckebach, 1928 ; Wenckebach, 1928) and pulmonary congestion is stated to occur only as a terminal condition (Wenckebach, 1928). In our case the combination of œdema and systemic congestion with gallop rhythm and pulmonary congestion showed that both right and left ventricles had failed.

2. *Ætiology.*—The absence of the more common causes of heart failure first drew attention to our case, and is probably one of the most valuable clinical pointers to the ætiology. There was no evidence of syphilitic, hypertensive or rheumatic heart disease or of heart failure secondary to pulmonary disease.

Other possible causes of œdema must be considered. In beri-beri heart the plasma proteins are sometimes lowered (Weiss and Wilkins, 1936) ; but usually not to such a level as would account for the œdema. In our case they were normal on the tenth day, and before the weight had reached a steady level. Severe anæmia is unusual in beri-beri heart, although common in other forms of œdema associated with dietary deficiency.

(3) *Diet.*—In our case, inquiry into the diet revealed a gross abnormality which left no doubt that a vitamin deficiency must have existed for a considerable time. To justify the assumption of a vitamin deficiency it is essential to establish a gross abnormality of this type. In this country chronic alcoholism is the most frequent cause of such a deficiency, and amongst the reported cases attributed to alcoholism are those of Jolliffe and Goodhart (1938), Price (1938) and many of those recorded by Weiss and Wilkins (1936 and 1937*a*).

(4) *Vitamin Therapy.*—The therapeutic test is the most convincing diagnostic evidence. Aalsmeer and Wenckebach (1928) thought the effect of vitamin B_1 to be as specific for beri-beri heart as thyroid extract is for myxœdema. Its

action is certainly no less dramatic. In our case, twenty-four hours after the first injection the pulse rate fell, the patient regained his appetite and a brisk diuresis set in.

Rapid response to treatment with vitamin B_1 has been recorded by Weiss and Wilkins (1936), Hashimoto (1937), Strauss (1938) and others. Weiss and Wilkins (1937*b*) state that, in general, the improvement is most rapid in patients with a severe degree of congestive failure of relatively short duration. Nylin (1937) recorded a case which responded very well to intravenous vitamin B_1, although complicated by bilateral pulmonary tuberculosis.

It is important to exclude the possibility that other forms of œdema or heart failure might respond to vitamin B_1 therapy. Weiss and Wilkins (1936) gave doses of 5, 10 and 20 mg. of crystalline vitamin B_1 subcutaneously, intramuscularly, and intravenously to two patients with normal cardiovascular systems, and to three with organic heart disease. They found no significant alternations in heart rate, electrocardiograms, arterial pressure, velocity of blood flow, plasma proteins or in the degree of œdema.

(5) *Other Signs of Vitamin Deficiency*.—These help to corroborate the diagnosis ; for instance, the presence of polyneuritis and heart failure, in an alcoholic subject, suggests the possibility of alcoholic beri-beri. The commonest associated lesions are polyneuritis and gastro-intestinal disturbances, particularly anorexia, epigastric pain, and vomiting. It is not unusual to find achlorhydria in beri-beri heart, as in the case recorded by Price (1938). Other common associated lesions mentioned by Weiss and Wilkins (1936) are pellagroid dermatitis and glossitis.

(6) *Special Tests*.—(*a*) The estimation of vitamin B_1 in the blood.—This assay has only recently been possible, and, so far as we know, has never yet been made in a case of beri-beri heart ; but there is little doubt that it will prove to be of value in these cases when there is better agreement as to the lower limit of the normal range. Wilkinson and Rowlands (1938) regard the threshold as about 6·5 μg per 100 c.c. using the effect of the vitamin on the growth of Phycomyces blakesleeanus (Schopfer's method) as the method of estimation.

(*b*) The peripheral circulation rate.—Weiss and Wilkins (1937*b*) state that the combined presence of congestive failure and a relatively or absolutely increased circulation rate is the most outstanding feature of beri-beri heart failure. It would seem, therefore, that the measurement of the peripheral circulation time is an investigation of value when this ætiology is suspected in a case of acute heart failure.

(*c*) Aalsmeer's Adrenalin Test.—This is regarded by many as a valuable diagnostic aid. It depends upon the rapid fall of diastolic pressure and the exacerbation of symptoms which follow the injection of adrenalin. Weiss and Wilkins (1936) record a case which demonstrates how this effect is striking in the acute stages and less so as the clinical condition improves.

(*d*) Electrocardiographic changes in the beri-beri heart have been described by many workers (Aalsmeer and Wenckebach, 1928 ; Scott and Hermann, 1928 ; Keefer, 1930 ; Hashimoto, 1937 ; Price, 1938 ; Wenckebach, 1928 ; Weiss and Wilkins, 1936 ; Strauss, 1938 ; and others) ; but these changes are

often absent, even in cases with advanced heart failure (Aalsmeer and Wenckebach, 1928), and, although the changes are reversible by treatment, they vary widely in character. The only feature of diagnostic value appears to be the shortening of the P-R interval described in a few cases by Aalsmeer and Wenckebach (1928) and by Price (1938). Chopra, Choudhuri, and De (1937) noted similar changes in 40 per cent. of cases of epidemic dropsy in India. It is only where the electrocardiogram shows changes reversible by vitamin B_1 therapy that it can be accepted as affording evidence of value in diagnosis. In our case, the electrocardiogram was within normal limits throughout, but the T wave in lead III, which was upright during the acute stage (Fig. 2), became inverted a month later. This was also noted in two cases by Keefer (1930), but we do not attach any significance to this finding.

Lesser Degrees of Vitamin B_1 Deficiency

If gross deficiency of vitamin B_1 can produce such striking cardiovascular disturbances, it seems probable that less severe deficiency, which must be much more common, often passes unrecognized, and may contribute to the development of cardiac failure in patients with rheumatic, syphilitic, or hypertensive heart disease. It is, therefore, important to inquire into the diet of patients with these forms of heart disease, especially when cardiac failure occurs without adequate cause.

Weiss and Wilkins (1937*a*) state that cardiovascular disturbances attributable to deficiency of vitamin B_1 occurred in 35 out of 5506 admissions to the Boston General Hospital medical wards during two years. They regard this form of cardiovascular disease as more frequent than congenital heart disease, adhesive pericarditis, hyper- or hypothyroid heart disease and subacute bacterial endocarditis. It is probable that some cases of beri-beri heart escape recognition, and that the heart failure is attributed to other causes.

Summary

A bar attendant, aged 36, with a history of chronic alcoholism and gross dietary deficiency, with anorexia, vomiting, epigastric pain, extensive œdema, a greatly enlarged heart, gallop rhythm and tachycardia, was treated with parenteral vitamin B_1. He lost his œdema and other signs of cardiac failure in five days, the heart diminished greatly in size, and he was discharged cured seventeen days after admission.

The case is compared with others that have been reported and the diagnosis of the condition is discussed.

We are indebted to our colleague Dr. E. W. Twining for the two radiograms.

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THE DRUG TREATMENT OF HYPERPIESIA

BY

WILLIAM EVANS AND OWEN LOUGHNAN

From the Cardiac Department of the London Hospital

Received April 2, 1939

The more numerous the remedies for a disease the less likely that any will prove consistently helpful. Of the many drugs recommended for hyperpiesia (essential hypertension) there is no agreement on the best to employ, and none has gained any outstanding reputation. There seems to be no authoritative statement on the comparative value of these remedies, and individual drugs have been praised without controlled clinical observations. The urge for trying new remedies in hyperpiesia is prompted by the common incidence of a condition which produces bizarre symptoms and determines many complications. Although for this reason treatment is a matter of great concern, it is not likely to be very successful while the cause remains unknown.

This paper deals primarily with the effects of certain drugs on the blood pressure in patients with hyperpiesia, and also records our observations on the influence of changes in the blood pressure on the subjective symptoms. We are not concerned here with the advisability of reducing blood pressure in hyperpiesia, but our findings during short periods of a lowered pressure have convinced us that the presence of symptoms has little or no relation to the level of the blood pressure. The opportunity, however, of observing the results of a greatly lowered blood pressure in hyperpiesia over a long period has only been gained through the onset of cardiac infarction or heart failure, when the appearance of newer symptoms might mask the direct effects of the lowered pressure.

METHOD OF OBSERVATION

We submitted the following preparations to clinical trial : sodium nitrite, glyceryl trinitrate, erythrol tetranitrate, mannitol hexanitrate, bismuth subnitrate, potassium iodide, iodine, potassium bromide, sodium luminal, chloral hydrate, papaverine sulphate, euphyllin, diuretin, theominal, doryl, pacyl, hypotan, calcium chloride, atropine, potassium thiocyanate, benzyl benzoate, guipsine, detensyl, phyllosan, citrin, yohimbine hydrochloride, padutin, vagotonine, angioxyl, bioglan H, anabolin, perandren, and œstrone. We selected these remedies either on account of a reputation which they already held in the treatment of hyperpiesia or on account of their pharmacological action in producing a fall in blood pressure. Many of the proprietary preparations were

enlisted for trial not with any faith in their reputed hypotensive qualities but for the purpose of comparing their effects with those of the active drugs. In this way we added to our controls.

The preparations were tried in 70 patients, 13 of whom were males and 57 females. The ages varied from 38 to 72 years and the average age was 58. Before admission into the series each patient was judged to be a case of hyperpiesia after a routine clinical examination which included urine analysis, tests of renal function, retinoscopy, electrocardiography, and radiocardioscopy. On radiocardioscopy, left ventricular enlargement and distortion of the aorta in the form of an unfolding were sought, and when either change preponderated it was noted. Any patient whose systolic blood pressure was less than 160 mm. Hg or whose diastolic blood pressure was less than 100 mm. was excluded from the series. Again, patients in whom a blood pressure of 160/100 was recorded at the first examination were not admitted unless they showed a rise above this at one of two other observations. Any patient with a systolic pressure of 200 mm. or over was not excluded simply because the diastolic pressure was less than 100 mm. No patient with evidence of nephritis was admitted. Any who failed to co-operate during the course of the investigation was rejected.

Each patient attended the London Hospital at fortnightly intervals, but whenever a drug required parenteral administration or closer observation of its effects he was admitted into hospital. At each attendance a resting period of half an hour or longer was assured before starting observations. Questions were then asked about progress during the trial period, any change in symptoms, the occurrence of untoward or toxic manifestations, and any variation in the patient's activity or habits which might influence the course of progress. The blood pressure was then taken (to the nearest multiple of 5 mm.) under conditions which were constant and standard for each patient. The investigation lasted for eighteen months, and over a thousand blood pressure readings were recorded, representing a similar number of observation periods each of a fortnight's duration. We came to place greater reliance on frequent controlled readings of the blood pressure in a limited number of co-operative patients, and so avoided retaining too many in the series.

The drugs were always given in adequate and usually in optimum doses, and this ensured that each patient was under the full influence of the drug soon after the start of the trial period. Although the *daily* dosage is instanced under each drug, it is to be understood that this was dispensed as three separate doses during the day. If symptoms of intolerance appeared it was discontinued, but was often given another trial after a suitable lapse of time. Although a single trial period usually permitted an opinion on the efficiency of a drug in reducing the blood pressure value, it was as a rule tried over several consecutive periods in a certain number of patients.

Before a remedy was judged to have established a claim to be of value as a hypotensive agent, it had to satisfy certain standards of efficiency. First, it had to be capable of reducing the blood pressure when this was raised and of maintaining it at the lower value. Secondly, it had to demonstrate this action

consistently and in a high proportion of patients, thus proving an effect distinct from the lowered pressure which occurs as a natural periodic variation in a patient with hyperpiesia without treatment. Thirdly, this reduction had to be obtained without any toxic symptoms.

It therefore became necessary to know the extent to which the blood pressure fluctuated naturally apart from the influence of any active drug. In a series of 650 school children of the ages of 10 to 17 years Lord Dawson (1925) found among 52 in whom the systolic pressure exceeded 130 mm. that this higher reading only remained consistently high in 17 per cent., while in the remaining 83 per cent. it was inconstant. To gain a knowledge of this natural variation in our patients we made use of frequent test periods when the patient was taking a simple placebo mixture, interspersed among test periods allotted to active drugs. The result of one such observation is charted in Fig. 1. Again, many

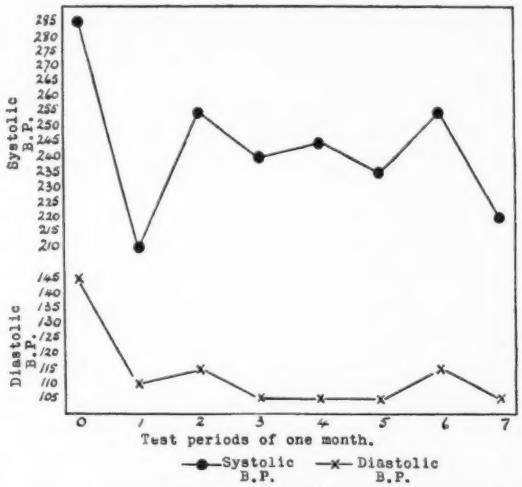

FIG. 1.—Blood pressure in a female, aged 58, with hyperpiesia, during a period of seven months when a placebo mixture was the only treatment given.

patients with hyperpiesia were observed throughout when taking only placebo mixtures, while some of those with obesity were observed during dietetic treatment and without medicine. In this way we feel that our evaluation of drugs used in the treatment of hyperpiesia, based as it is on strictly controlled observations, is substantially accurate. The second part of Fig. 2 illustrates the scheme of our observations during successive test periods of 14 days on the different drugs ; the first part showing the effect of a reducing diet (see later).

RESULTS

If the blood pressure did not rise or fall at the end of a test period by more than 10 mm., we regarded it as showing no change. If the blood pressure fell

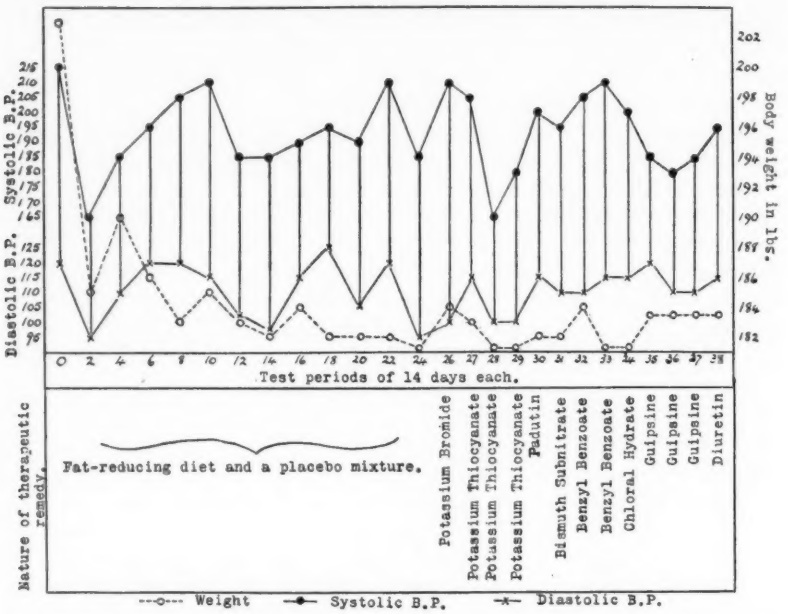

FIG. 2.—Blood pressure in a male, aged 57, with hyperpiesia, during treatment with a fat-reducing diet and later with certain active drugs.

by 10 mm. during successive observation periods, when statistically it would continue to be regarded as showing no change, we recorded it as showing a fall in the second instance. If a rise or fall of 11 to 25 mm. occurred, we have classified it as a moderate; and if of 26 mm. or over, as a conspicuous change. These figures apply to the systolic pressure, because we found that it was the more dependable figure upon which to judge the variation. The diastolic figure usually showed the same kind of change as the systolic, but not to the same extent, while its exact estimation could not be determined as readily as the systolic. If perchance a prominent change in the diastolic value was not also shown in the systolic value, we were careful to record it.

NITRITES

The effects of sodium nitrite on the blood pressure in healthy subjects and in patients with hyperpiesia were observed by Weiss and Ellis (1933); a fall usually occurred within 5 to 15 minutes after 1 to 5 grains had been taken by mouth, and averaged 12 mm. for 30 minutes in the healthy subjects and 35 mm. for two hours in the patients with hypertension.

A transient fall in the blood pressure follows the administration of amyl nitrite. Zeiss and Brams (1930) observed the action of amyl nitrite and glyceryl trinitrate on the blood pressure in 10 patients with hyperpiesia and in 10 healthy subjects. Amyl nitrite produced a fall in each of these cases, and glyceryl

trinitrate (1/50 grain by mouth) reduced it temporarily in the healthy subjects but not always in the patients with hyperpiesia. The effects of the two drugs were also noted by Burgess (1931) ; amyl nitrite reduced the blood pressure in both groups, but glyceryl trinitrate, in doses of 1/100 to 1/50 grain by mouth or 1/200 grain subcutaneously, did not produce a constant effect.

In successive papers Stieglitz (1927, 1928, 1930, and 1932) has extolled the value of bismuth subnitrate as a vasodilator and as a hypotensive agent in patients with hyperpiesia. He postulated that the beneficial effect depended on the gradual vasodilatation resulting from the continuous absorption of small quantities of nitrite ions and a reduction of the blood chloride which follows the diuretic action of the nitrate ion. Ayman (1932) tried bismuth subnitrate in daily doses of 30 grains for periods of three to nine months in 15 patients with hyperpiesia ; his observations were carefully controlled and he concluded that the drug had not lowered the blood pressure in a single case. Bruen (1932) observed the hypotensive action of bismuth subnitrate in healthy subjects, and in 1934 was able to report on such a trial in a series of patients with hyperpiesia. The observations were carefully controlled, so that periods on lactose tablets and oxalate powders were compared with periods on 30, 60, and 90 grains of bismuth subnitrate daily. He concluded that bismuth subnitrate was without influence on either the blood pressure or the symptoms.

Amyl Nitrite.—We observed the effect on the blood pressure of inhalation of amyl nitrite (5 minims) in 22 patients with hyperpiesia and in 18 healthy subjects. There was a fall in both systolic and diastolic pressure in each of the 40 cases, but the change was more noticeable in the former. In the patients with hyperpiesia the systolic fall varied from 10 to 100 mm., and averaged 45 mm. The average time before the fall took place was one minute and its average duration was three minutes. A compensatory rise of an average of 22 mm. only followed in four instances (Fig. 7). In the healthy subjects the systolic fall varied from 10 to 60 mm. and averaged 33 mm. The average time before the fall took place was one minute and its average duration was six minutes. A compensatory rise of an average of 36 mm. followed in four instances.

Glyceryl Trinitrate.—We also observed the effects on the blood pressure when this was *chewed* in tablets containing 1/100, 1/50, 1/25, and 1/12 grain, in 7 patients with hyperpiesia and in 5 healthy subjects. A fall in both systolic and diastolic pressure occurred in each of the 12 cases. The systolic fall was the more noticeable, and in the hypertensive group varied from 25 to 195 mm. with an average of 55 mm. The average time before the fall took place was 6 minutes and its average duration was 16 minutes. In the healthy subjects the fall varied from 15 to 40 mm. with an average of 26 mm. The average time before the fall took place was 4 minutes and its average duration 16 minutes. A compensatory rise of the blood pressure value was not seen in either group.

Inhalation of amyl nitrite and the chewing of glyceryl trinitrate will therefore always cause the systolic blood pressure to fall, both in normals and in patients with hyperpiesia, the extent of the fall being greater in the latter. The fall produced with glyceryl trinitrate appears later than with amyl nitrite, but the effect lasts longer. The transient changes indicate that amyl nitrite and glyceryl

trinitrate are unlikely to prove of value in the continuous treatment of hyperpiesia.

Sodium nitrite was submitted to a controlled clinical trial in 19 patients with hyperpiesia, and its effect observed in a daily dosage of 15 grains (0·9 g.) during 22 test periods.* A moderate fall occurred during 2 test periods, but it did not persist when the drug was continued. There was no change during 6, and a moderate rise took place during 6 test periods ; in 8 the effect could not be recorded as the patients failed to continue taking the drug.

Symptomatic improvement was recorded during 3 test periods on sodium nitrite, but during 19 the symptoms either remained stationary or became aggravated. Toxic effects, namely giddiness, palpitation, headache, and weakness occurred in 13, and in 8 the symptoms compelled the patients to discontinue its use.

Glyceryl trinitrate was tried in 11 patients with hyperpiesia, and its effect observed in a daily dosage of 1/33 grain (0·0018 g.) given by mouth during 11 test periods. A fall occurred during 2 test periods, conspicuous in one and moderate in the other. There was no change during 1, and a rise took place during 4, conspicuous in 1 and moderate in 3. The effects could not be recorded in 4 instances as the patients failed to take the tablets because of faintness, giddiness or palpitation.

Symptomatic improvement was recorded during 1 test period on glyceryl trinitrate, but during 10 the symptoms either remained stationary or became aggravated.

Erythrol tetranitrate was tried in 13 patients with hyperpiesia, and its effect observed in a daily dosage of 1½ grains (0·09 g.) during 19 test periods. A fall occurred during 7, conspicuous in 5 and moderate in 2 ; there was no change during 6 ; and a rise took place during 6, conspicuous in 1 and moderate in 5.

Symptomatic improvement was recorded during 6 test periods on erythrol tetranitrate, but during 13 the symptoms either remained stationary or became aggravated. Toxic effects, namely giddiness and headache, occurred twice.

Mannitol hexanitrate was tried in 24 patients with hyperpiesia, and its effect observed in a daily dosage of 6 grains (0·36 g.) during 29 test periods. A fall occurred during 8, conspicuous in 4 and moderate in 4 ; there was no change during 5 ; and a rise took place during 9, conspicuous in 1 and moderate in 8. In 7 it was not possible to record its effects because the patients failed to continue taking the drug on account of dizziness and headache.

Symptomatic improvement was recorded during 6 test periods on mannitol hexanitrate, but during 23 the symptoms either remained stationary or became aggravated.

Bismuth subnitrate was tried in 22 patients with hyperpiesia, and its effect observed in a daily dosage of 60 grains (3·6 g.) during 39 test periods. A fall occurred during 8, conspicuous in 3 and moderate in 5 ; there was no change during 17 ; and a rise took place during 14, conspicuous in 5 and moderate in 9.

Symptomatic improvement was recorded during 24 test periods on bismuth

* A test period means in each case a period of 14 days.

subnitrate, but during 15 the symptoms either remained stationary or became aggravated. Toxic effects were not seen.

A comparison of these results with those obtained from placebo treatment is made in Table I.

TABLE I

COMPARING THE EFFECTS OF NITRITES AND PLACEBO ON THE BLOOD PRESSURE AND ON THE SYMPTOMS IN PATIENTS WITH HYPERPIESIA

Drug	Number of Test Periods	Change in Blood Pressure Value			Effect on Symptoms	
		Fall	No Change	Rise	Improved	Not improved or worse
Sodium nitrite ..	22 (60)	14 (30)	43 (57)	43 (13)	14 (33)	86 (67)
Glyceryl trinitrate ..	11 (27)	28 (37)	15 (48)	57 (15)	10 (40)	90 (60)
Erythrol tetranitrate	19 (38)	36 (42)	32 (39)	32 (19)	32 (37)	68 (63)
Mannitol hexanitrate	29 (59)	36 (34)	23 (55)	41 (11)	20 (36)	80 (64)
Bismuth subnitrate	39 (40)	20 (30)	44 (65)	36 (5)	61 (33)	39 (67)

Figures, excepting those in the first column, denote percentage of test periods. Figures in brackets apply to the placebo mixture.

IODINE

Potassium iodide intravenously often causes the blood pressure to fall, but Macht (1914) showed that its hypotensive effect was due to potassium and not the iodine ion. Mosenthal (1933) obtained hypotensive effects from the use of sodium and potassium iodide in daily doses of 3 to 10 grains in cases of hypertension. The use of iodine in hyperpiesia is also mentioned by others (Norris, Bazett, and McMillan, 1927 ; Gager, 1930 ; Hay, 1931 ; Parkinson, 1936 ; White, 1937). Livingstone (1935) advocated the use of Lugol's iodine. Lewis (1937), speaking on drugs used in hyperpiesia, said that none offered much prospect of benefit and that even potassium iodide, which had long been favoured as a remedy, was losing its reputation in this field.

Iodine, as Lugol's solution, was tried in 20 patients with hyperpiesia, and its effect observed in a daily dosage of 18 minims (1·1 c.c.) during 42 test periods. A moderate fall occurred during 5 test periods ; there was no change during 28 ; and a rise during 9, conspicuous once and moderate in 8.

Symptomatic improvement was recorded during 18 test periods on iodine, but during 24 the symptoms either remained stationary or became aggravated.

Potassium iodide was submitted to a controlled clinical trial in 23 patients with hyperpiesia, and its effect observed in a daily dosage of 30 grains (1·8 g.) during 28 test periods. A fall occurred during 4 test periods, conspicuous in 1 and moderate in 3 ; there was no change during 19 ; and a rise took place during 5, conspicuous in 4 and moderate once.

Symptomatic improvement was recorded during 10 test periods on potassium iodide, but during 18 the symptoms either remained stationary or became aggravated.

A comparison of these results with those obtained from placebo treatment is made in Table II.

TABLE II

COMPARING THE EFFECTS OF IODINE AND PLACEBO ON THE BLOOD PRESSURE AND ON THE SYMPTOMS IN PATIENTS WITH HYPERPIESIA

Drug	Number of Test Periods	Change in Blood Pressure Value			Effect on Symptoms	
		Fall	No Change	Rise	Improved	Not improved or worse
Iodine	42 (53)	10 (26)	67 (57)	23 (17)	43 (30)	57 (70)
Potassium iodide ..	28 (53)	14 (29)	68 (48)	18 (23)	36 (30)	64 (70)

Figures, excepting those in the first column, denote percentage of test periods. Figures in brackets apply to placebo.

SEDATIVES

Bromide.—We have not found reports of any observations on the effects of bromide on the blood pressure in hyperpiesia, but its use has been mentioned especially in connection with the relief of symptoms (Gager, 1930 ; Hay, 1931 ; Parkinson, 1936 ; White, 1937).

Potassium bromide was tried in 40 patients with hyperpiesia, and its effect observed in a daily dosage of 30 grains (1·8 g.) during 66 test periods. A fall occurred during 21, conspicuous in 8 and moderate in 13 ; there was no change during 29 ; and a rise took place during 16, conspicuous in 6 and moderate in 10.

Symptomatic improvement was recorded during 27 test periods on potassium bromide, but during 39 the symptoms either remained stationary or became aggravated.

Sodium Luminal.—Gruber and others (1925) gave luminal in daily doses of 4½ grains to 36 patients with hypertension, and found a fall in pressure in 85 per cent., but the degree of this fall is not given, and it was not maintained on prolonged administration. Hay (1931) attributed to luminal a slight hypotensive as well as sedative effect, but this action was evanescent and was more likely to prove beneficial in early cases. Parkinson (1936) favoured luminal along with bromide in relieving symptoms, particularly palpitation and restlessness. Adson and Allen (1937) regarded sedatives, especially the barbiturates, as the most valuable drugs in high blood pressure, and stated that under controlled conditions it fell to normal in many patients, and that the dosage should be adjusted to secure a sedative action without causing drowsiness.

We submitted sodium luminal to trial in 38 patients with hyperpiesia, and observed its effect in a daily dosage of 1½ grains (0·09 g.) during 52 test periods. A fall occurred during 14, conspicuous in 5 and moderate in 9 ; there was no change during 26 ; and a rise took place during 12, conspicuous in 2 and moderate in 10.

Symptomatic improvement was recorded during 21 test periods on sodium luminal, but during 31 the symptoms either remained stationary or became aggravated. Toxic effects were not seen.

Chloral Hydrate.—Matte and Dias-Cavaroni (1926) reported on an investigation of the effects of certain drugs on the blood pressure in cases of hyperpiesia. They found that chloral hydrate frequently reduced the systolic pressure, but that this effect seldom lasted more than ten days.

We submitted chloral hydrate to a trial in 23 patients with hyperpiesia, and observed its effect in a daily dosage of 30 grains (1·8 g.) during 33 test periods. A fall occurred during 10 test periods, conspicuous in 4 and moderate in 6; there was no change during 17 ; and a rise took place during 5, conspicuous in 2 and moderate in 3. In one instance the effect could not be recorded, because of dizziness and headache.

Symptomatic improvement was recorded during 7 test periods on chloral hydrate, but during 26 the symptoms either remained stationary or became aggravated.

Papaverine Sulphate.—Reporting on an experimental study of papaverine sulphate, Macht (1916) stated that it slowed the heart rate and reduced the blood pressure through vasodilatation of the peripheral arteries. The use of opium was mentioned by Norris, Bazett, and McMillan (1927), and White (1937) mentioned papaverine in the treatment of hyperpiesia, but expressed no opinion as to its value.

We submitted papaverine sulphate to a trial in 16 patients with hyperpiesia, and observed its effect in a daily dosage of 7½ grains (0·45 g.) during 24 test periods. A fall occurred during 8, conspicuous in 4 and moderate in 4; there was no change during 13 ; and a moderate rise took place during 3.

Symptomatic improvement was recorded during 6 test periods on papaverine sulphate, but during 18 the symptoms either remained stationary or became aggravated. Toxic effects were not seen.

A comparison of these results with those obtained from placebo treatment is made in Table III.

TABLE III

COMPARING THE EFFECTS OF SEDATIVE DRUGS AND PLACEBO ON THE BLOOD PRESSURE AND ON THE SYMPTOMS IN PATIENTS WITH HYPERPIESIA

Drug	Number of Test Periods	Change in Blood Pressure			Effect on Symptoms	
		Fall	No Change	Rise	Improved	Not improved or worse
Potassium bromide	66 (90)	32 (31)	44 (52)	24 (17)	41 (34)	59 (66)
Sodium luminal ..	52 (90)	27 (31)	50 (51)	23 (18)	40 (30)	60 (70)
Chloral hydrate ..	33 (43)	30 (29)	55 (56)	15 (15)	20 (30)	80 (70)
Papaverine sulphate	24 (31)	34 (42)	54 (46)	12 (12)	25 (32)	75 (68)

Figures, excepting those in the first column, denote percentage of test periods. Figures in brackets apply to placebo.

Xanthine Derivatives

The xanthine derivatives have been mentioned in connection with the treatment of hyperpiesia by Livingstone (1935), White (1937), and Lewis (1937), but without an opinion on their actual value as hypotensive agents. Calcium diuretin, in the experience of Basch (1924), caused the blood pressure in hypertension to fall at times as much as 40 mm. and to remain at the lowered figure ; and Kaiser (1925) also obtained good results from it.

We submitted *euphyllin* (theophylline-ethylene-diamine) to a trial in 31 patients with hyperpiesia, and observed its effect in a daily dosage of 9 grains (0·6 g.) during 41 test periods. A fall occurred during 11 test periods, conspicuous in 4 and moderate in 7 ; there was no change during 23 ; and a rise took place during 7, conspicuous in 2 and moderate in 5.

Symptomatic improvement was recorded during 10 test periods on euphyllin, but during 31 the symptoms either remained stationary or became aggravated. Toxic effects, namely weakness, insomnia, headache, and palpitation occurred twice.

We submitted *diuretin* (theobromine-sodio-salicylate) to a trial in 26 patients with hyperpiesia, and observed its effect in a daily dosage of either 30 grains (1·8 g.) or 45 grains (2·7 g.) during 30 test periods. A fall occurred during 5 test periods, conspicuous in 1 and moderate in 4 ; there was no change during 16 ; and a rise took place during 4 test periods, conspicuous in 1 and moderate in 3. In 5 instances the effects could not be recorded because the patients failed to continue taking the drug on account of giddiness, headache and sickness. These symptoms were also present in three others and were more noticeable with the larger dose.

Symptomatic improvement was recorded during 4 test periods on diuretin, but during 26 the symptoms either remained stationary or became aggravated.

A comparison of the results of these drugs and theominal with those obtained from placebo treatment is made in Table IV.

TABLE IV

Comparing the Effects of Drugs belonging to the Xanthine Group and Placebo on the Blood Pressure and on the Symptoms in Patients with Hyperpiesia

Drug	Number of Test Periods	Change in Blood Pressure Value			Effect on Symptoms	
		Fall	No Change	Rise	Improved	Not improved or worse
Euphyllin	41 (81)	27 (31)	56 (54)	17 (15)	24 (33)	76 (67)
Diuretin	30 (64)	20 (30)	64 (57)	16 (13)	13 (33)	87 (67)
Theominal	21 (48)	23 (40)	53 (44)	24 (16)	33 (31)	67 (69)

Figures, excepting those in the first column, denote percentage of test periods. Figures in brackets apply to placebo.

We submitted *theominal* (sodium luminal and theobromine) to a trial in 16 patients with hyperpiesia, and observed its effect in a daily dosage of 30 grains

(1·8 g.) during 21 test periods. A moderate fall occurred during 4 test periods ; there was no change during 9 ; and a rise took place during 4, conspicuous in one and moderate in 3.

Symptomatic improvement was recorded during 7 test periods on theominal, but during 14 the symptoms either remained stationary or became aggravated. Toxic effects, namely giddiness or drowsiness, occurred four times, and compelled the patients to discontinue its use.

Choline Derivatives

Acetylcholine.—A fall in blood pressure as a result of vasodilatation was shown in the cat by Dale (1914) after small doses of this intravenously. Wolff (1929) was also able to show vasodilatation in organs supplied by the parasympathetic nervous system and a generalized dilatation of the cutaneous arterioles. Meakins and Scriven (1931) recorded a fall of from 25 to 40 mm. in 72 per cent. of their observations on seven cases of hypertension following intramuscular injections of 0·1 to 0·2 g. of acetylcholine ; the effect lasted from one to four hours. Only three out of thirteen healthy subjects showed an appreciable fall in blood pressure after intravascular administration of 2 per cent. acetylcholine given at the rate of 0·02 to 0·14 g. per minute (Ellis and Weiss, 1932). Carmichael and Fraser (1933) gave it intravenously in doses of from 0·01 to 0·03 g. to 46 subjects, and cardio-inhibitory effects appeared within five to ten seconds,but lasted only a few seconds. The slowing of the heart rate was followed by an acceleration, and the systolic and diastolic pressure fell during the phase of slow heart rate, but returned to normal or even higher during the phase of increased heart rate. More recently Fraser (1938) stated that the administration of acetylcholine in man gave disappointing therapeutic results ; when given intravascularly the effects are too brief, and when given intramuscularly too uncertain.

Doryl (carbaminoyl-choline) and Mecholin (acetyl-β-methyl-choline) are more stable than acetylcholine and are active even when given by mouth. Their hypotensive properties have been demonstrated by Kreitmair (1932), Dautrebande (1933) and Fraser (1938), but Fraser has pointed out that both preparations are valueless in the treatment of hyperpiesia, except for the relief of hypertensive headache. Pacyl is another choline derivative which is said to be active when given by mouth. Lewy (1928) and Ganter (1928) reported hypotensive effects and symptomatic improvement from its use. The preparation hypotan is a mixture of methylacetylcholine, bromocholine bromide and chloral hydrate. Its use in hypertension has been recommended on account of its alleged action as a vasodilator.

We submitted *doryl* to a controlled clinical trial in 11 patients with hyperpiesia, and observed its effect in a daily dosage of 6 tablets during 12 test periods. A temporary moderate fall occurred during 1 test period ; there was no change during 4 ; and a rise took place during 3 test periods, conspicuous in 2 and moderate in 1. The effect could not be recorded in 4 instances because the patients failed to continue taking the preparation.

Symptomatic improvement was recorded during 3 test periods on doryl, but during 9 the symptoms either remained stationary or became aggravated. Toxic effects, namely sweating, weakness, giddiness and nausea, occurred in 5 instances.

Pacyl was tried in 11 patients with hyperpiesia, and its effect on the blood pressure in a daily dosage of 6 tablets observed during 22 test periods. A fall occurred during 4, conspicuous in 2 and moderate in 2 ; there was no change during 15 ; and a rise took place during 3, conspicuous in 1 and moderate in 2.

Symptomatic improvement was recorded during 10 test periods on pacyl, but during 12 the symptoms either remained stationary or became aggravated.

Hypotan was tried in 19 patients with hyperpiesia, and its effect observed in a daily dosage of 8 tablets during 36 test periods. A fall occurred during 10, conspicuous in 3 and moderate in 7 ; there was no change during 16 ; and a rise took place during 10, conspicuous in 5 and moderate in 5.

Symptomatic improvement was recorded during 14 test periods on hypotan, but during 22 the symptoms either remained stationary or became aggravated.

A comparison of these results with those obtained from placebo treatment is made in Table V.

TABLE V

COMPARING THE EFFECTS OF ACETYLCHOLINE DERIVATIVES AND PLACEBO ON THE BLOOD PRESSURE AND ON THE SYMPTOMS IN PATIENTS WITH HYPERPIESIA

Drug	Number of Test Periods	Change in Blood Pressure Value			Effect on Symptoms	
		Fall	No Change	Rise	Improved	Not improved or worse
Doryl	12 (34)	12 (41)	50 (53)	38 (6)	25 (47)	75 (53)
Pacyl	22 (22)	18 (32)	68 (63)	14 (5)	46 (45)	54 (55)
Hypotan	36 (39)	27 (38)	45 (54)	28 (8)	39 (38)	61 (62)

Figures, excepting those in the first column, denote percentage of test periods. Figures in brackets apply to placebo.

OTHER CHEMICAL DRUGS

Calcium Chloride.—The neutralizing action of calcium and potassium chloride on the pressor substances of the guanidine series was mentioned by Major (1925). Addison and Clark (1925) treated 45 patients with hypertension with calcium chloride in daily doses of 90 to 180 grains, and found a persistent fall of 30 mm. or more in the systolic pressure and of 12 mm. or more in the diastolic pressure in 26 cases. Altnow and O'Hare (1927) used calcium chloride and atropine in the treatment of 11 cases with hypertension ; no fall in pressure was noticed in 6 and it was insignificant in the remaining 5 patients.

Calcium chloride was tried in 20 patients with hyperpiesia, and its effect observed in a daily dosage of 90 grains (6 g.) during 25 test periods. A fall

occurred during 4, conspicuous in 1 and moderate in 3 ; there was no change during 11 ; and a rise took place during 6, conspicuous in 2 and moderate in 4. In 4 other instances it was not possible to record the effects because of a burning taste in the mouth, sickness or epigastric pain.

Symptomatic improvement was recorded during 6 test periods on calcium chloride, but during 19 the symptoms either remained stationary or became aggravated.

Atropine.—This has been recommended for hypertension on the assumption that raised blood pressure is the outcome of an unbalanced action in the autonomic system, so that the vagal action preponderates over the sympathetic. Altnow and O'Hare (1927) treated 11 patients with calcium chloride and atropine, but without any change in 6 and with an insignificant change in the remaining 5. Norris, Bazett, and McMillan (1927) stated that experimentally atropine raises the blood pressure through stimulation of the vasoconstrictor centre and raising the pulse rate, but that this pressor effect was rarely met with clinically. White (1937) also mentioned the use of atropine in hypertension.

We submitted atropine sulphate to a trial in 9 patients with hyperpiesia, and observed its effect in a daily oral dosage of 1/20 grain (0·003 g.) during 9 test periods. A moderate fall occurred during 1 test period ; there was no change during 5 ; and a rise took place during 2, conspicuous in 1 and moderate in another. In one instance it was not possible to record the effects because of dryness of the mouth and mistiness of vision, and these symptoms were also present in 6 others who persisted with the drug.

Symptomatic improvement was recorded during 3 test periods on atropine sulphate, but during 6 the symptoms either remained stationary or became aggravated.

Potassium Thiocyanate (potassium rhodanate).—During a clinical trial of the effects of cyanate in patients suffering from neurasthenia, Pauli (1903 and 1904) observed both a reduction in the pressure and an improvement of symptoms when hypertension was present. Nichols (1925) stated that the drug was excreted slowly and that cumulative effects might appear ; it was, however, excreted unchanged without the formation of the poisonous prussic acid radicle. Therapeutically he found it reduced the blood pressure to a greater extent than any other drug in hyperpiesia. Smith and Rudolf (1928) gave sodium sulphocyanate to five healthy subjects and to 72 cases with hypertension, the daily dose for one group being 5 grains, for another 10 grains and for a third 15 grains A fall in blood pressure occurred in each of the healthy subjects and each of the patients with hypertension, and the change was more noticeable in the latter. They observed a fall of as much as 100 mm. in the systolic pressure, and as a rule the greater fall followed the greater dosage. Better results were obtained in those patients without evidence of renal damage and in those who showed the least amount of arterial changes from atheroma. No severe toxic symptoms were noticed. Gager (1928) observed the effects of smaller doses (4½ grains or less daily) of sulphocyanate in 25 patients with hyperpiesia. It was lowered in 22, sometimes by 20 to 60 mm. The fall in the diastolic pressure was not as conspicuous. Subjective improvement was often recorded. Palmer, Silver,

and White (1929) using the same dosage as Gager in 59 cases of hyperpiesia found a reduction of 30 mm. or more in the systolic pressure in 42 per cent. Fineberg (1930), comparing the effects of thiocyanate and sedatives, found that the blood pressure was more often reduced by thiocyanate, but that greater subjective improvement followed sedatives. During controlled observations in 25 patients, Egloff, Hoyt, and O'Hare (1931) obtained a favourable response twice only. Treatment of 99 patients with hypertension with sulphocyanate in doses varying from 5 to 15 grains daily over periods up to three years resulted in a reduction of blood pressure in 68 per cent. (Bolotin, 1932). Both Palmer (1932) and Goldring and Chassis (1932) found that thiocyanate reduced the pressure in 31 per cent. of cases ; but Palmer found it did not persist and that often where it had fallen initially with treatment a retrial failed to reproduce this effect. Goldring and Chassis found toxic symptoms in 17 per cent. of their cases, and two deaths were attributed to the drug. A fall in the pressure was noted by Ayman (1931) in 20 of 31 cases with hyperpiesia, but in 19 out of the 20 it was accompanied by distressing toxic symptoms, both in large doses over short periods and in small doses over longer periods. Barker (1936 and 1937) stressed the importance of estimating the cyanate content of the blood during treatment, and thought the optimum benefit occurred when it was maintained at 8 to 12 mg. per 100 c.c.; when it reached 15 to 30 mg. toxic symptoms appeared. The standard concentration in the blood was never obtained by a constant cyanate dosage. He stated that if the concentration was maintained at a suitable level, a fall in blood pressure and symptomatic improvement would be expected in 50 per cent. of cases. When this standard concentration was maintained in 16 patients with hypertension, Griffith and Lindauer (1937) found that both the systolic and diastolic blood pressure became lowered in 10 with improvement of general symptoms and without any severe toxic effects. Massie, Ethridge, and O'Hare (1938) gave sodium thiocyanate to 14 patients with hyperpiesia, under controlled conditions, and found it reduced the pressure and improved the symptoms.

We submitted potassium thiocyanate to a trial in 38 patients with hyperpiesia, and observed its effect in a daily dosage of 4½ grains (0·3 g.) during 90 test periods. A fall occurred during 34, conspicuous in 11 and moderate in 23 ; there was no change during 36 ; and a rise took place during 20, conspicuous in 6 and moderate in 14.

Symptomatic improvement was recorded during 31 test periods on potassium thiocyanate, but during 59 the symptoms either remained stationary or became aggravated. Toxic effects were not seen.

Benzyl Benzoate.—Macht (1918), as the result of experiments in animals, found this diminished the tonicity of smooth muscle, and decided on a clinical trial in intestinal colic, bronchial spasm and angiospasm. Using 45 minims of a 20 per cent. alcoholic solution daily he claimed good results in 100 cases, including many with hyperpiesia. Later Macht (1920) reaffirmed his opinion on its beneficial effects and gave further examples in which a raised blood pressure had been reduced by the daily administration of from 60 to 90 minims of the 20 per cent. alcoholic solution. These observations were not con-

trolled and the proportion responding successfully was not expressed. Laubry and Mougeot (1921) submitted benzyl benzoate to a clinical trial and concluded that it was a useful drug to combine with others because it gave results which were sometimes surprising, rarely negligible, and never harmful. Gruber and Shackelford (1924) gave 120 minims of the 20 per cent. alcoholic solution of benzyl benzoate daily for periods of four to eighteen days to 16 patients with hyperpiesia. Their observations were carefully controlled and appeared to show that when given by mouth it had no effect on the raised pressure in hyperpiesia.

We submitted benzyl benzoate to a trial in 30 patients with hyperpiesia, and observed its effect in a daily dosage of 24 minims (1·6 mils) during 45 test periods. A fall occurred during 7 test periods, conspicuous in 3 and moderate in 4 ; there was no change during 23 ; and a rise took place during 15, conspicuous once and moderate in 14 instances.

Symptomatic improvement was recorded during 15 test periods, but during 30 the symptoms either remained stationary or became worse.

A comparison of these results with those obtained from placebo treatment is made in Table VI.

TABLE VI

COMPARING THE EFFECTS OF CALCIUM CHLORIDE, ATROPINE SULPHATE, POTASSIUM THIOCYANATE, AND BENZYL BENZOATE WITH THOSE OF A PLACEBO ON THE BLOOD PRESSURE AND ON THE SYMPTOMS IN PATIENTS WITH HYPERPIESIA

Drug	Number of Test Periods	Change in Blood Pressure Value			Effect on Symptoms	
		Fall	No Change	Rise	Improved	Not improved or worse
Calcium chloride ..	25 (43)	18 (32)	54 (58)	28 (10)	24 (37)	76 (63)
Atropine sulphate ..	9 (30)	12 (42)	64 (46)	24 (12)	33 (33)	67 (67)
Potassium thiocyanate	90 (88)	37 (36)	40 (50)	23 (14)	34 (31)	66 (69)
Benzyl benzoate ..	45 (61)	16 (39)	51 (48)	33 (13)	33 (34)	67 (66)

Figures, excepting those in the first column, denote percentage of test periods. Figures in brackets apply to placebo.

SOME VEGETABLE EXTRACTS

Guipsine.—This is a preparation of mistletoe which has been advocated on account of its alleged action as a vasodilator of the peripheral arterioles.

Guipsine was tried in 12 patients with hyperpiesia, and its effect observed in a daily dosage of 9 pills during 19 test periods. A fall occurred during 6, conspicuous in 1 and moderate in 5 ; there was no change during 9 ; and a rise took place during 4, conspicuous once and moderate in 3 instances.

Symptomatic improvement was recorded during 4 test periods on guipsine, but during 15 the symptoms either remained stationary or became worse.

Detensyl.—This consists of extracts of mistletoe, liver, pancreas and lung ; and because a hypotensive action from vasodilatation has been ascribed to each of these constituents it has sometimes been recommended.

We submitted detensyl to a trial in 14 patients with hyperpiesia, and observed its effect in a daily dosage of 4 tablets during 18 test periods. A fall occurred during 4 test periods, conspicuous in 1 and moderate in 3 ; there was no change during 9 ; and a rise took place during 4, conspicuous in 1 and moderate in 3. One patient failed to take the tablets.

Symptomatic improvement was recorded during 6 test periods on detensyl, but during 12 the symptoms either remained stationary or became aggravated.

Phyllosan is the name given to a concentrated extract of chlorophyll obtained from green vegetables. Originally recommended in the treatment of anæmia, it has recently been accredited with hypotensive effects, but on such meagre evidence that we accepted it into our series for additional control observations.

We submitted phyllosan to a trial in 9 patients with hyperpiesia, and observed its effect in a daily dosage of 6 tablets during 16 test periods. A moderate fall occurred during 4 ; there was no change during 9 ; and a rise took place during 2 test periods, conspicuous in one and moderate in another. The effect could not be recorded in one patient because he was unable to take this medicine on account of giddiness.

Symptomatic improvement was recorded during 5 test periods, but during 11 the symptoms either remained stationary or became worse.

Citrin (*cucurbocitrin*).—Barksdale (1926) isolated an active principle from the seed of the water-melon which belongs to the group of glucoside-saponins and which prove on experiment to dilate the smaller arteries. Barksdale claimed good results in 10 cases of nephritic hypertension. In 68 patients in whom the blood pressure was raised, Wilkinson (1927) found a fall with symptomatic improvement in 82 per cent. Cucurbocitrin was given by Althausen and Kerr (1929) in daily doses of 150 to 450 mg. to 40 patients with hypertension. An immediate fall in pressure was noticed and its extent appeared to be directly dependent on the dosage. After prolonged administration an average fall of 29 mm. in the systolic and of 15 mm. in the diastolic pressure occurred in 73 per cent. of the cases, while symptomatic improvement was recorded in even more ; toxic symptoms were never noted. Gargill and Rudy (1931) treated 29 cases of hyperpiesia with cucurbocitrin and found it of no value ; in only 7 instances was the systolic pressure reduced by 25 mm., a reduction which might occur spontaneously. Seward (1931) prescribed it in 16 patients in doses varying from 150 to 200 mg. daily. The blood pressure was reduced in 4 after treatment for fourteen days, and this effect lasted for some time and went with symptomatic improvement. Later he (1932) reported that in 9 out of 22 cases the systolic pressure was reduced by 30 mm. and the diastolic by 10 mm. following treatment with citrin in doses of from 300 to 400 mg. daily.

We submitted citrin to a trial in 13 patients with hyperpiesia, and observed its effect in a daily dosage of 300 mg. during 13 test periods. A fall occurred during 2 test periods, conspicuous in 1 and moderate in 1 ; there was no change during 7 ; and a rise took place during 2, conspicuous in 1 and moderate in 1. In 2 instances the patients were unable to continue taking the medicine.

Symptomatic improvement was recorded during 4 test periods on citrin, but during 9 the symptoms either remained stationary or became aggravated.

Toxic effects, namely headache, insomnia and a sense of choking, occurred in 3 instances.

Yohimbine, an alkaloid obtained from yohimbine bark, is a peripheral vasodilator, and produces a small hypotensive effect. It is said to augment the action of other agents, and Loeper and Lemaire (1930) found that in dogs previously treated with yohimbine, the hypotensive effects of acetylcholine were four times as great. Barrieu (1932) reported good results from such a combination when given to patients. Taken with phenylethyl-barbituric acid it was favoured by Busquet and Vischniac (1935).

We submitted yohimbine hydrochloride to a trial in 16 patients with hyperpiesia, and observed its effect in a daily dosage of 1/3 grain (0·02 g.) during 18 test periods. A moderate fall occurred during 3 ; there was no change during 6 ; and a moderate rise took place during 5. In 4 instances the patients could not continue taking the drug.

Symptomatic improvement was recorded during 4 test periods on yohimbine, but during 14 the symptoms either remained stationary or became worse. Toxic effects, namely trembling, shivering, dizziness, and headache, occurred in six instances.

Some Animal Extracts and Hormones

Padutin, originally known as kallikrein, is a pancreatic extract. It is alleged to contain a vasomotor hormone with hypotensive properties when given either by mouth or by intramuscular injection, and it is standardized by physiological methods. A fall in blood pressure was observed by Leschke (1930) in patients with hyperpiesia when taking padutin. In some the fall was considerable and persistent, while in others it was slight and transient. Scharpff (1931) compared the effects on the blood pressure of rest and a restricted diet, with and without padutin. A fall in pressure occurred in both groups, but was more noticeable in those taking padutin, where the average fall in the systolic and diastolic values was 64 and 31 mm. as against an average fall of 35 and 5 mm. in patients not taking padutin. Subjective improvement was also recorded. Nuzum, Elliot, and Bischoff (1937) gave kallikrein hypodermically in ten patients ; they controlled their results and found a fall in pressure in only two patients while the symptoms remained unchanged. Wolffe and others (1937) observed the effects of de-insulinated pancreatic extract in 150 patients with hypertension. A fall in systolic and diastolic pressure occurred in 108, and in 8 of these it was conspicuous ; symptomatic improvement was noticed in 62 per cent. and lasted for over twelve months. In the remaining 42 the changes were comparable with those observed in a control series.

We submitted padutin to a trial in 36 patients with hyperpiesia, and observed its effect in a daily dosage of 60 minims (3·6 c.c.) during 46 test periods. A fall occurred during 9 test periods, conspicuous in 5 and moderate in 4 ; there was no change during 21 ; and a rise took place during 16, conspicuous in 5 and moderate in 11.

Symptomatic improvement was recorded during 17 test periods on padutin, but during 29 the symptoms either remained stationary or became aggravated.

Vagotonine is obtained from the pancreas, and its specific physiological action is said to be one antagonizing the action of adrenaline and restraining its secretion ; through its action on the sympathetic system it reduces vasomotor tonicity. Abrami, Santenoise, and Bernal (1933) recorded a fall in the blood pressure in 42 of 80 cases of hypertension after subcutaneous injections of 20 or more often 40 mg. of vagotonine. If a fall did not occur within two hours of the first injection, they did not expect any reduction from daily injections even when repeated on twenty consecutive days ; on the other hand, the fall which commenced within two hours was maintained from 12 to 48 hours. Urticaria was sometimes seen.

We observed the effects of a subcutaneous injection of 0·02 g. of vagotonine in 6 patients with hyperpiesia, and in one of these the injection was repeated. Frequent blood pressure readings were taken before and after the injection for a period not less than two hours, and further readings were recorded on subsequent days. We also had evidence of the variation in the blood pressure value during periods of treatment with active drugs or placebo mixtures. In none of our 6 patients was the blood pressure lowered, either immediately or more remotely, by injections of vagotonine and indeed it was at a higher level after the injection in 4 of them. We concluded that vagotonine had no place in the treatment of hyperpiesia, for in the patients in whom it was given a trial it produced no hypotensive effects. In one patient it gave rise to very severe urticaria.

Angioxyl is an insulin-free extract of pancreas which is standardized physiologically. It has been claimed that it antagonizes the action of adrenaline and that it produces vasodilatation, resulting in a lowering of the blood pressure.

We submitted it to a trial in 10 patients with hyperpiesia, and observed its effect in a daily dosage of 80 units during 15 test periods. A fall occurred during 5, conspicuous in 3 and moderate in 2 ; there was no change during 5 ; and a rise took place during 4, conspicuous in 2 and moderate in 2. In one instance the patient had failed to take the medicine on account of headache.

Symptomatic improvement was recorded during 5 test periods on angioxyl, but during 10 the symptoms either remained stationary or became aggravated.

Bioglan H consists of a concentration of hormones obtained from pancreas, anterior pituitary and human placenta. In 20 cases of hypertension selected from the druggist's laboratory files it is recorded that an average blood pressure of 210/117 before treatment became 158/91 after treatment, and this reduced value had persisted for a year after the initial course of injections.

One c.c. of bioglan H was injected intramuscularly twice weekly for three weeks in four female patients with hyperpiesia, and for two weeks in a male patient. Daily blood pressure readings were taken under controlled conditions and when these were considered it was found that in no instance had it caused any reduction.

A comparison of the results of these preparations and of anabolin with those obtained from placebo treatment is made in Table VII.

TABLE VII

COMPARING THE EFFECTS OF 8 PREPARATIONS WITH THOSE OF A PLACEBO ON THE BLOOD PRESSURE AND ON THE SYMPTOMS IN PATIENTS WITH HYPERPIESIA

Drug	Number of Test Periods	Change in Blood Pressure			Effect on Symptoms	
		Fall	No Change	Rise	Improved	Not improved or worse
Guipsine	19 (24)	30 (28)	50 (64)	20 (8)	21 (40)	79 (60)
Detensyl	18 (38)	24 (37)	53 (52)	23 (11)	33 (37)	67 (63)
Phyllosan	16 (13)	26 (24)	60 (69)	14 (7)	33 (46)	67 (54)
Citrin	13 (29)	18 (31)	64 (52)	18 (17)	29 (35)	71 (65)
Yohimbine hydrochloride ..	18 (42)	21 (23)	42 (61)	37 (16)	22 (33)	78 (67)
Padutin	46 (75)	20 (32)	45 (59)	35 (9)	37 (34)	63 (66)
Angioxyl	15 (20)	33 (45)	41 (35)	26 (20)	34 (25)	66 (75)
Anabolin	35 (52)	18 (24)	61 (61)	21 (15)	20 (27)	80 (73)

Figures, excepting those in the first column, denote percentage of test periods. Figures in brackets apply to placebo.

Anabolin is an extract of liver isolated by alcohol fractionation methods, and its introduction into clinical medicine in the treatment of hyperpiesia has depended on its specific action as a vasodilator. Its pharmacological action in lowering blood pressure in the experimental animal is constant and uniform, so that solutions containing it can be standardized by this method. Major (1924 and 1925) appeared to show that hypertension could be induced experimentally by the introduction of guanidine bases, and because he was able to reduce this rise by the administration of liver extract he postulated that its hypotensive action did not depend solely on vasodilatation, but that it also assisted the liver in destroying pressor bodies in the form of amino-acid waste products. Later (1926) in 100 patients with hypertension he reported that an immediate fall in the blood pressure could be obtained from liver extract injections, and that this effect was often conspicuous and lasted for several hours. MacDonald (1925) gave the results obtained from the treatment of 33 patients with hyperpiesia. Lautman (1926) reported a fall in blood pressure in 34 cases of hypertension following 10 to 24 daily injections of liver extract. Harrower (1926) recorded a fall in blood pressure in 40 cases of hypertension from the use of anabolin (1 to 4 tablets daily) by mouth. Burnett (1926) expressed his opinion that the hypotensive effects of liver extract depended mainly on the histamine which it contained, and in 1929, with Althausen and Kerr, he described favourable results from the use of intramuscular injections in 27 cases with hypertension. Willis (1930) has described the preparation and standardization of anabolin and has stated that it is free from choline and that histamine is only present in negligible quantities. When used intravenously in 150 cases of hyperpiesia it invariably lowered the blood pressure and produced symptomatic improvement, but the same favourable results were not obtained from its oral administration.

We submitted anabolin to a trial in 22 patients with hyperpiesia, and

observed its effect in a daily dosage of 3 tablets by mouth during 35 test periods. A fall occurred during 6, conspicuous in 3 and moderate in 3 ; there was no change during 20 ; and a rise took place during 7, conspicuous in 4 and moderate in 3. In 2 instances the effects could not be recorded because the patients failed to continue taking anabolin on account of dizziness.

Symptomatic improvement was recorded during 7 test periods on anabolin, but during 28 the symptoms either remained stationary or became aggravated.

Sex Hormones.—Steinach, Peczenik, and Kun (1938) investigated the action of male hormone preparations on male patients with hypertension, and noted a fall in the systolic pressure in 31 of 49 cases treated with androsterone benzoate or testosterone propionate. Symptomatic improvement also took place. In a further series small doses of œstradiol benzoate were added to the male hormone. They found that cases which proved refractory to the male hormone alone responded favourably to the combined preparation. Steinach and Kun (1937) believed that the male hormone was converted into an œstrogenic substance when injected into male patients, and they attributed clinical improvement in male patients with hypertension to the converted male hormone.

Perandren (male hormone) and œstrone (female hormone) were given consecutively by intramuscular injections of 1 c.c. twice weekly for three weeks in 8 patients with hyperpiesia, 4 of whom were males and 4 females. Frequent blood pressure readings were recorded, and comparing these with those obtained during control periods on a placebo mixture we concluded that neither preparation evoked any hypotensive effect.

WEIGHT-REDUCING DIET IN HYPERPIESIA

Embleton (1938) recorded a steady and lasting fall in blood pressure in 18 patients with hyperpiesia while taking a high-protein diet which caused reduction in the body weight. He mentioned, however, that transitory rises in the pressure took place on account of constipation or severe emotional strain. His claims were based on a comparison of subsequent blood pressure readings with the initial reading. The present investigation has convinced us of the necessity of discarding the first and sometimes even the second reading in order to avoid the fallacious deductions which inevitably result if these are accepted as values standard for the patient. In 28 out of 64 unselected cases of hyperpiesia in this series we found that the blood pressure at the second examination after placebo treatment did not vary by more than 10 mm. from that recorded at the first examination, but in 36 cases a variation of more than 25 mm. had occurred ; in 9 it had risen and in 27 it had fallen. Not only did a fall take place three times more often than a rise, but the extent of the fall was much greater than the rise ; thus only 3 cases showed a rise exceeding 40 mm. and none exceeded 60 mm., whereas among the 27 cases where a fall had taken place it was 40 mm. or over in 11 cases and in 5 of these it was 60 mm. or over.

We determined the effects of a reducing diet in 5 patients with hyperpiesia and obesity during a period when no active drugs were prescribed. The daily diet, providing for equal values of protein, fat and carbohydrate, had a calorie value of about 1168 calories, and was made up as follows :

Breakfast : Tea with milk. Two eggs or a piece of fish or one thin rasher of bacon. Vita-weat biscuit. Butter (size of a cherry). Tomatoes or fresh fruit (¼ lb.).

Dinner : A good portion of lean meat or cheese. Plateful of green vegetables or salad. One small apple, orange, pear, or grapefruit. Vita-weat biscuit.

Tea : Tea with milk. One egg. Vita-weat biscuit and butter (size of a cherry).

Supper : A fair portion of steamed fish or lean meat or cheese. Plateful of green vegetables or salad. Vita-weat biscuit and butter (size of two cherries). One small apple, orange, pear, or grapefruit.

Sugar, cakes, pastries, puddings, jam, bread, potatoes, bananas, and fried food were not allowed.

A satisfactory reduction of body weight was always obtained within a short period and details of this and the blood pressure readings have been set out in charts (Figs. 3, 4, 5 and 6). When these results were compared with

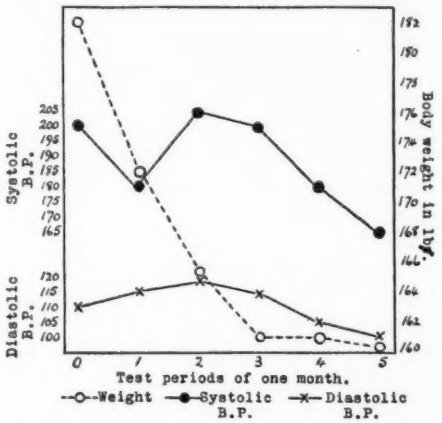

FIG. 3.—Blood pressure in a female, aged 59, with hyperpiesia, during treatment with a fat-reducing diet.

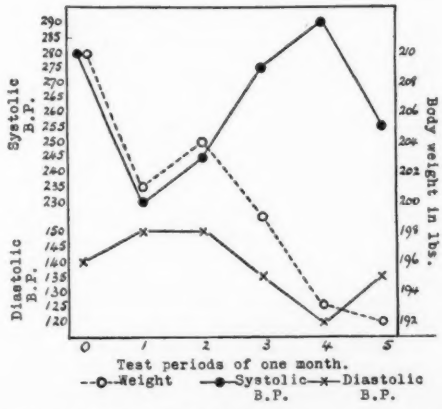

FIG. 4.—Blood pressure in a female, aged 53, with hyperpiesia, during treatment with a fat-reducing diet.

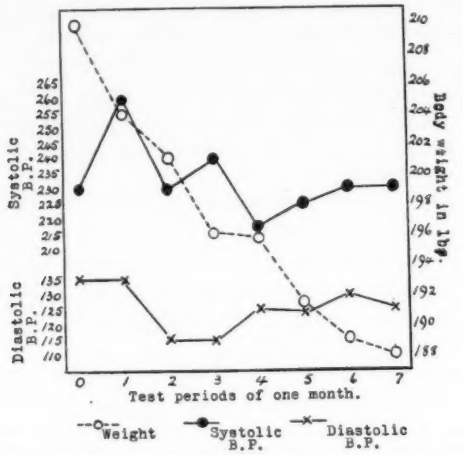

FIG. 5.—Blood pressure in a female, aged 48, with hyperpiesia, during treatment with a fat-reducing diet.

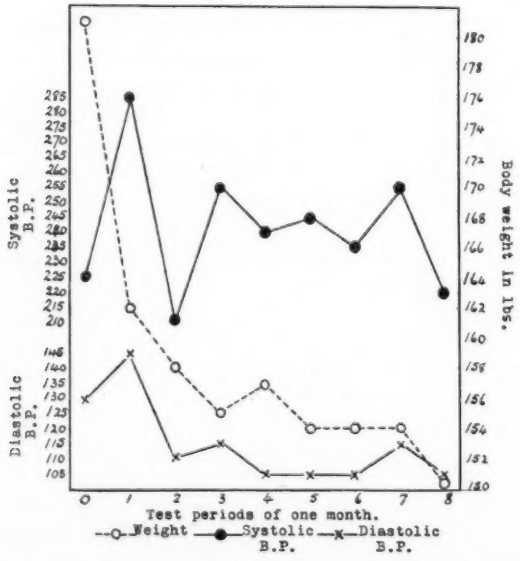

FIG. 6.—Blood pressure in a female, aged 68, with hyperpiesia, during treatment with a fat-reducing diet.

those obtained from the use of a placebo only (Fig. 1), we concluded that dietetic treatment which effected a considerable reduction in the body weight did not influence the blood pressure in patients with hyperpiesia, although symptomatic improvement from loss of weight usually took place. During the period when the weight was falling quickly and later when the reduced weight was being maintained the blood pressure showed a variation which we have come to regard as a normal occurrence in a patient with hyperpiesia (Fig. 1). Observations in these five obese patients undergoing dietetic treatment have in this way provided us with another opportunity of watching this natural variation.

DISCUSSION OF RESULTS

Natural Variation in Blood Pressure

Although we knew that the blood pressure fluctuates from time to time, becoming higher during periods of nervousness, as this investigation proceeded we came to realize more fully how great is the natural variation and how false would be the judgment of the hypotensive action of a drug if this were ignored. No drug should be credited with such properties unless it has exerted this effect to a greater extent than that which occurs naturally during a period on placebo treatment. Fig. 1 shows these periodic changes in the blood pressure during a time when a placebo medicine was the only form of treatment. Similar variations are seen in Figs. 2 to 6 in patients on a reducing diet and a placebo.

Again, the initial blood pressure, i.e. the first reading, is often so much higher than the standard for the individual patient that a disregard of this fact has led to a wrong estimate of the hypotensive properties of certain drugs. Thus among those patients in whom a second reading differed from the first by more than 25 mm. while on placebo treatment there was a fall in three-quarters of the cases. Frequently the systolic value fell 40 mm. and often more than 60 mm. (see Table VIII). We attributed the higher initial readings to the

TABLE VIII

CHANGE IN THE BLOOD PRESSURE AT THE SECOND EXAMINATION WHEN TAKING A SIMPLE PLACEBO MIXTURE

Data	Blood Pressure Change		
	No Change or Change of less than 10 mm.	Rise	Fall
Sixty-four patients with hyperpiesia	28	9	27
Change in systolic blood pressure in mm.	—	15 15 25 20 20 15 40 45 50	20 15 25 25 20 15 15 25 25 20 20 20 25 15 25 20 50 60 75 40 40 40 65 65 60 45 45

excitement at the first clinical examination, and sought confirmation of this by recording the pressure continuously in 7 healthy subjects and in 7 patients with hyperpiesia until it assumed a constant and basic level as they rested on the examining couch. The extent of the fall and the time taken to reach this level is shown in Table IX. The effect of emotional disturbance on the blood

TABLE IX

THE FALL IN BLOOD PRESSURE TO ITS BASIC LEVEL WITH REST ON AN EXAMINATION COUCH. THE BLOOD PRESSURE WAS RECORDED EACH MINUTE

Case	Initial State of the Blood Pressure	Extent of Fall of Systolic Pressure in mm. before reaching a Constant Basic Level	Time (in minutes) taken to reach Basic Level
1	Raised	20	6
2	Raised	55	19
3	Raised	30	5
4	Raised	5	2
5	Raised	10	6
6	Raised	10	4
7	Raised	10	7
8	Normal	20	20
9	Normal	15	2
10	Normal	30	9
11	Normal	5	1
12	Normal	25	6
13	Normal	10	4
14	Normal	10	10

pressure was next observed in patients at rest and just after a verbal explanation about amyl nitrite inhalation. A rise in the blood pressure invariably took place and within two minutes of the explanation (Table X and Fig. 7). Such changes are of obvious importance in considering the effect of a drug.

TABLE X

THE RISE OF SYSTOLIC BLOOD PRESSURE AFTER EXPLAINING THE DETAILS CONNECTED WITH AMYL NITRITE INHALATION

Case	Initial State of the Blood Pressure	Extent in mm. to which the Systolic Blood Pressure Rose within Two Minutes of the Explanation
1	Raised	25
2	Raised	10
3	Raised	25
4	Raised	10
5	Raised	10
6	Raised	5
7	Raised	10
8	Normal	20
9	Normal	20
10	Normal	30
11	Normal	25
12	Normal	15
13	Normal	15
14	Normal	35
15	Normal	15

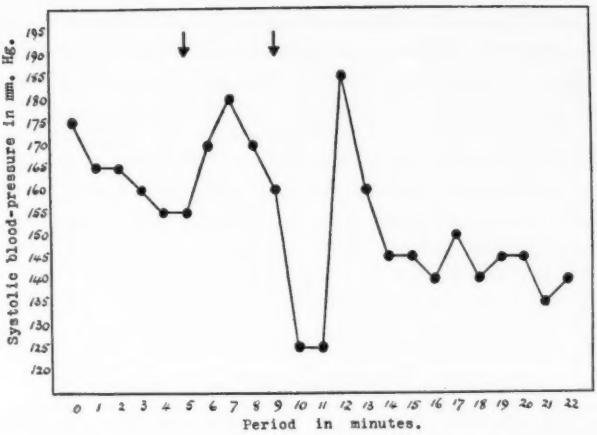

FIG. 7.—Showing the reaction of the blood pressure to emotional disturbance and to inhalation of amyl nitrite. The blood pressure, which has taken four minutes to fall to its basic level, rises following an explanation of the procedure of amyl nitrite inhalation, falls abruptly after the inhalation, and maintains a low level following a temporary and reactionary rise. The first arrow in the chart indicates the stage at which the explanation was made and the second arrow denotes the time of the inhalation.

Effect of Drugs on the Blood Pressure

Not until our records were completed did we examine the results critically, and then it was apparent that although these patients had been taking continuously the many reputed remedies none showed any clinical change nor any effective fall in blood pressure. It never assumed a value during treatment with any of the 33 remedies tried that was lower than the value recorded in the same patient when an inert placebo was exhibited. It is remarkable that even when considered statistically (see Table XI) in terms of hypotensive effects estimated from the relative incidence of the fall and rise in blood pressure while taking the different remedies, papaverine sulphate and chloral hydrate were the only two drugs producing collective results a trifle better than an inert placebo, and not enough to justify their routine use in hyperpiesia. No evidence was obtained to justify the prescribing of any of the tested preparations if the object is to reduce the blood pressure, for it has been shown here that none of them possesses this property under clinical conditions. The indiscriminate use of new and often expensive remedies for hypertension without first submitting them to a *controlled* clinical trial is to be deprecated.

Effect of Drugs on Symptoms

The effects of a blood pressure variation were watched particularly where a rise or fall of more than 25 mm. had taken place. During 64 test periods when this conspicuous change was a rise the symptoms improved in 36 per cent., were unchanged in 38 per cent. and were worse in 26 per cent. During 90 test periods when the change was a fall the symptoms improved in 34 per cent., were unchanged in 46 per cent. and were worse in 20 per cent. The symptoms in a patient with hyperpiesia, therefore, bear no relation to the height of his blood pressure at the time. It caused some surprise to find no improvement in such a high proportion of patients when the pressure had fallen conspicuously, and it caused greater surprise to find improvement in symptoms coinciding with a rise as often as with a fall in the blood pressure.

TABLE XI

SUMMARIZING THE CHANGES IN BLOOD PRESSURE IN PATIENTS WITH HYPERPIESIA DURING TEST PERIODS WHILE TAKING DIFFERENT MEDICINES

Medicine	Number of patients	Number of Test Periods each of 14 days	Change in Blood Pressure (expressed as percentage of the test periods)		
			Fall	No change	Rise
PLACEBO	**59**	**131**	**28**	**52**	**20**
Sodium nitrite	19	22	14	43	43
Glyceryl trinitrate	11	11	28	15	57
Erythrol tetranitrate	13	19	36	32	32
Mannitol hexanitrate	24	29	36	23	41
Bismuth subnitrate	22	39	20	44	36
Potassium iodide	23	28	14	68	18
Iodine	20	42	10	67	23
Potassium bromide	40	66	32	44	24
Sodium luminal	38	52	27	50	23
Chloral hydrate	23	33	30	55	15
Papaverine sulphate	16	24	34	54	12
Euphyllin	31	41	27	56	17
Diuretin	26	30	20	64	16
Theominal	16	21	23	53	24
Doryl	11	12	12	50	38
Pacyl	11	22	18	68	14
Hypotan	19	36	27	45	28
Calcium chloride	20	25	18	54	28
Atropine	9	9	12	64	24
Potassium thiocyanate	38	90	37	40	23
Benzyl benzoate	30	45	16	51	33
Guipsine	12	19	30	50	20
Detenzyl	14	18	24	53	23
Phyllosan	9	16	26	60	14
Citrin	13	13	18	64	18
Yohimbine hydrochloride	16	18	21	42	37
Padutin	36	46	20	45	35
Angioxyl	10	15	33	41	26
Anabolin	22	35	18	61	21

An estimate was made of the symptomatic improvement gained by patients under treatment with the various remedies. The improvement was always assessed by a comparison with progress shown during test periods on a placebo. Improvement greater than that shown during placebo treatment was only found in six of the active drugs, bismuth subnitrate, iodine and iodide, bromide, sodium luminal, theominal and potassium thiocyanate. Excepting bismuth subnitrate, they only proved slightly superior to a placebo. In patients manifesting nervousness, restlessness and sleeplessness, bromide, sodium luminal and theominal often ameliorated the symptoms, but without any associated effect on the blood pressure.

SUMMARY AND CONCLUSIONS

The effect of 33 preparations on the blood pressure and symptoms was watched in 70 patients with hyperpiesia (essential hypertension) over a period of eighteen months. The drugs or preparations were various and included nitrites, iodides, sedatives, xanthine and choline derivatives, vegetable extracts and hormones. Naturally it was not possible to test each remedy in every patient as some were accepted after the investigation had begun and a few failed to complete the whole course. Each medicine was prescribed in optimum doses for test periods of a fortnight, and at the end of each period the patient attended for re-examination, when the blood pressure was recorded under the same unvarying and standard conditions and any change in symptoms was noted.

When the basic pressure for each patient had been estimated from the first three observations, the hypotensive effect (or absence of effect) of a particular drug was often decided in individual patients at the end of a test period of 14 days, but as a rule each drug was given a second trial over longer intervals in a certain number of patients. To begin with, and later at irregular intervals, control test periods were instituted for each patient, when an inert placebo mixture was the only treatment given. In two patients the blood pressure was recorded throughout the investigation while taking a placebo of which the colour and flavour were the only variants. In five obese patients it was recorded while on a reducing diet and without drugs.

After allowance had been made for the tendency to obtain high blood pressure readings at the first and possibly at the second examination, and for the natural variation, and when the results from the tested drugs were compared with those from a placebo, we found that none of the 33 preparations produced hypotensive effects in patients with hyperpiesia. In regard to symptomatic improvement, only 6 of the drugs, namely bismuth subnitrate, iodine and iodide, bromide, sodium luminal, theominal and potassium thiocyanate, on an average relieved symptoms rather more than did the placebo. The sedative drugs seem to have value in temporarily relieving nervous symptoms when these were prominent.

Although these results may surprise some, they will accord with the expectation and experience of many physicians. Admittedly, this paper deals with only a small section of the therapeutics of hyperpiesia, and it does not bear on the management of hypertensive heart disease including heart failure, where drug treatment can often be seen at its best. Our negative findings with drugs in uncomplicated hyperpiesia do not make it less desirable that the patient should remain under medical supervision. It is obvious that a patient should not regard his symptoms as closely related to the height of his blood pressure. Medical attention must be devoted to the alleviation of symptoms when they arise and to correcting faults in living, and particularly to the adoption of timely active measures when symptoms or signs of heart failure first appear.

Time will show whether surgical measures are a practicable means of lowering blood pressure and of lessening symptoms in hyperpiesia. Meantime a clearer insight into the origin of hypertension must precede its successful treatment with drugs.

We are grateful to Mr. C. H. Sykes, pharmacist to the hospital, who willingly co-operated with us throughout the investigation. Our thanks are due to Messrs. Ciba, Ltd., for supplying perandren and œstrone. We are indebted for financial assistance : one of us (W. E.) received a grant from the Medical Research Council, and the other (O. L.) held a scholarship from the Medical Research Council of Ireland, tenable under the direction of Professor Arthur Ellis of the Medical Unit, London Hospital. Dr. John Parkinson, Physician to the Cardiac Department, has helped us with advice and criticism.

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ELECTROCARDIOGRAPH ELECTROLYTES

BY

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Received April 6, 1939

The contact with the body needed for electrocardiographic purposes is often made by wrapping a few layers of gauze soaked in saline round the limb and binding over that a metal electrode. This method has the disadvantages that the limb to limb resistance is rather high and increases considerably as the gauze dries. Also the bedclothes must be protected from becoming wet when an electrocardiogram has to be taken from a bedridden patient.

If the limb to limb resistance is high the string of the Einthoven galvanometer must be slackened to increase the sensitivity, and so the record may be distorted by the alteration of the damping and the reduction of the natural frequency of the string (Pardee, 1917). In the case of valve electrocardiographs, with their high input resistance—usually about 100 times that of the string—high body resistance is not so disadvantageous ; but if it can be kept low there is less likelihood of electrical interference, and in addition the stability of the amplifier is increased.

We were led to consider these points recently while carrying out some cardiac tolerance tests by a method described previously (Bell and Knox, 1938). As some of our experiments lasted more than an hour the drying of the saline pads was a great handicap. We therefore tried soft green soap, as used by Boas (1928) under similar circumstances, and found that it fitted our requirements admirably.

Although skin resistance has often been investigated in connection with chronaxie and the psychogalvanic reflex, we could find no report of a systematic investigation into the properties of electrolytes, apart from the work of Hartridge (1931) which dealt with the effect of grease-removing substances. It was thought, therefore, that it would be interesting to compare soft green soap with certain other electrolytes.

METHOD

The electrolytes investigated were :

1. One per cent. sodium chloride in tap-water.
2. Soft green soap (Sapo Mollis Viridis, B.P.) which consists chiefly of an almost neutral mixture of potassium oleate with a little glycerine.

3. Cambridge electrode jelly, which is sold by the Cambridge Instrument Co. ; the composition of this substance is not issued.

4. A paste described by Jenks and Graybiel (1935), which we shall call for convenience Boston paste ; it consists mainly of sodium chloride, glycerine, water, and powdered pumice.

In the case of the first electrolyte, two layers of gauze bandage soaked in saline were wrapped round the forearms. Plymet electrodes each 14 cm. by 5 cm. were laid on the volar surfaces and held in place by rubber bands. Plymet is a soft sheet metal (supplied by Schall and Son, New Cavendish St., London, W.1), consisting mainly of lead, which is readily moulded to the shape of the arm.

In the case of Cambridge jelly a piece of the jelly about the size of the fingernail was rubbed into the forearms for about ten seconds, as recommended by Russell (1935). The Plymet electrodes were then smeared with the jelly, put directly on the skin, and held in place with bandages and rubber bands. The soft green soap and Boston paste were applied in a similar manner.

As is well known, there are some quick changes (rise and fall of R wave) and some slow changes (T wave) in the electrocardiogram. Hence an adequate description of the behaviour of an electrolyte should include both the D.C. resistance and the A.C. impedance.

The measurements were made by means of a bridge in which the subject formed one arm, and a variable resistance with a variable capacitance in parallel formed the second arm ; the ratio arms were formed by two equal resistances of 1000 ohms. Alternating current was supplied to the bridge by a valve oscillator which gave about 8 volts at 300 cycles per second (c.p.s.). A sensitive vibration galvanometer tuned to 300 c.p.s. was used to find the balance condition. The values of resistance and capacitance in the second arm, combined vectorially, gave the A.C. impedance, Z.

Thus $$Z=\frac{r}{\sqrt{1+\omega^2C^2r^2}}, \text{ where } \omega=2\pi f.$$

When the A.C. measurement had been made, an 8-volt battery was substituted for the oscillator and a moving coil galvanometer for the vibration galvanometer and the bridge brought once more to balance by varying the resistance in the second arm. This gave the direct current resistance, R.

Results

The wide scatter of the results, which are collected together in Fig. 1, is not altogether surprising in an experiment of this nature. As it was not, of course, possible to get simultaneous values for the different electrolytes, they were applied in turn, varying the order with each subject.

The values of Z were distributed over a considerable range. One per cent. sodium chloride gave, on the whole, the lowest values (average 652 ohms), Boston paste gave slightly higher values (average 689 ohms), whilst green soap and Cambridge jelly both gave still higher values (average 768 and 754 ohms respectively).

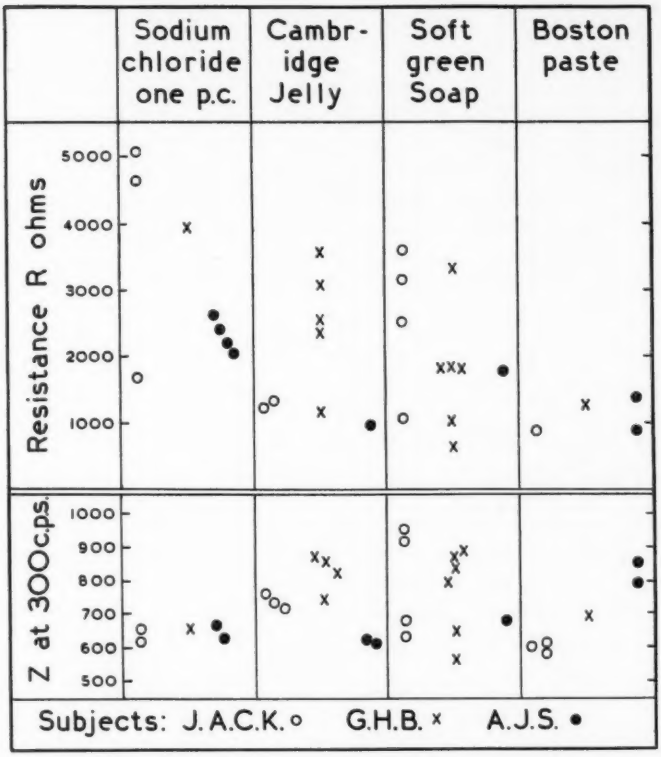

FIG. 1.—Chart of all the observations of body resistance from forearm to forearm for the three subjects with the four different electrolytes.

R was found to be highest with 1 per cent. sodium chloride, the average value being 3080 ohms. Cambridge jelly and green soap gave the somewhat lower average values of 2010 and 2040 ohms respectively. Boston paste gave the lowest average resistance of 1100 ohms.

In order to allow of further discrimination between the solid electrolytes, variation of R and Z with time was investigated. The electrodes were left in position for varying times up to one and three quarter hours and Z and R, in that order, were measured at quarter-hour intervals. The leads were removed from the bridge between readings. In all cases Z and R rose steadily, but not very greatly, for about three quarters of an hour after application of the electrodes, when the values became nearly constant (see Fig. 2).

DISCUSSION

From the wide scatter of the results shown in Fig. 1 it will be seen that it is not at all easy to choose the best electrolyte on the basis of Z and R values only.

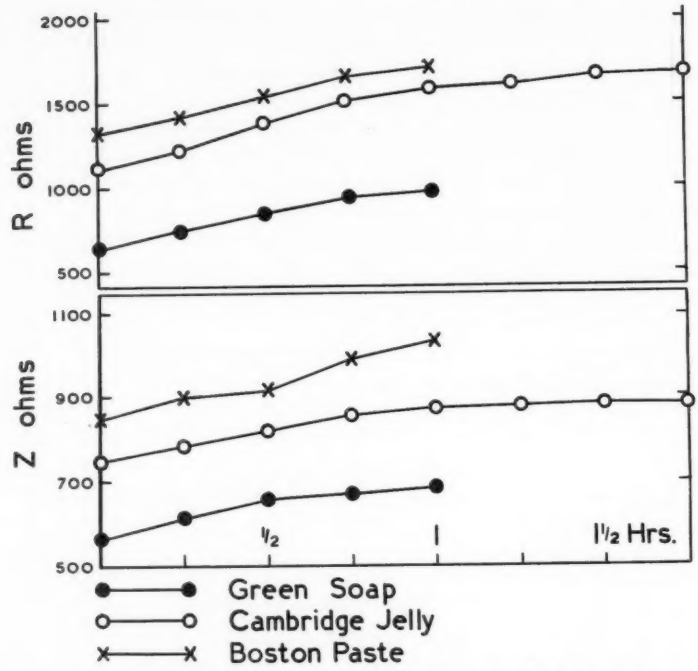

FIG. 2.—Variation of resistance (forearm to forearm) with time. Cambridge jelly and Green soap, subject G. H. B., Boston paste, subject A. J. S.

The best is probably Boston paste. Green soap and Cambridge jelly are only slightly inferior ; sodium chloride, on account of its very high R, is the poorest.

Drying up of the solid electrolytes does not occur to any great extent because none of them show any great increase in resistance up to one hour or more after application. There was no difference between electrocardiograms taken by means of a string galvanometer using first green soap and then Cambridge jelly. The choice between the three solid electrolytes will, therefore, have to be made on other grounds.

As green soap is a standard British Pharmacopœial substance and costs only about one penny per oz., it is to be preferred to the complicated Boston paste or the expensive Cambridge jelly.

THE EFFECT OF ABRASIVES

Boston paste is made up with a considerable proportion of powdered pumice, which at first we regarded merely as an inert base required to form the paste. But examination of Cambridge jelly points to a different conclusion. It appears to consist chiefly of sodium chloride in a base which is probably not lanoline or petroleum jelly, but which may be a gum. The jelly feels gritty to

the touch, and on dissolving away the base in hydrochloric acid an insoluble residue remains, which under the microscope proves to consist of extremely jagged particles of crushed quartz.

It is now clear why the jelly should be rubbed into the skin ; the sharp particles remove the surface cells and so contact is made with a deeper layer. Richter (1926, *a* and *b*) showed that a minute puncture of the skin below electrodes one inch square reduced R from 540,000 ohms to 15,000 ohms. Lewis and Zotterman (1927) came to the conclusion that the high resistance displayed by skin to galvanic currents resided in the superficial and horny layer. Accordingly it was decided to investigate the effects of abrasion quantitatively.

Method and Results

To one sample of green soap we added pumice in the proportion occurring in Boston paste and to another sample crushed quartz recovered from Cambridge jelly.

In these experiments the average value with green soap alone for Z was 885 ohms and for R was 2450 ohms. After rubbing in green soap with quartz the average values were Z 665 ohms and R 890 ohms, a decrease of 25 per cent. in Z and 64 per cent. in R. Rubbing in green soap with pumice left Z unchanged but reduced R by 57 per cent. Green soap covers the quartz and pumice particles and interferes with their abrasive qualities. It occurred to us, therefore, that it would be more effective to abrade the dry skin and then apply the electrolyte and electrode. The surface of the skin was rubbed gently two or three times with fine glass paper (No. 1). This raised the surface layer of cells so that the skin lost its sheen and became white in colour. This procedure resulted in a reduction of Z by 60 per cent. and of R by 80 per cent. on the average, the mean values after such abrasion being : Z, 400 ohms, and R, 500 ohms, approximately. These are the lowest values which we have observed during the whole course of this investigation.

In addition to the alteration of Z and R brought about by abrasion, it was noted in measuring Z that the resistive component required for balance fell to about one-half, or less, of the value before abrasion. The capacitance in parallel, however, fell to about one-tenth. For example, in one experiment before abrasion the bridge was balanced by 1790 ohms in parallel with 0·386 mfd., i.e. Z=1090 ohms ; after abrasion, balance was given by 368 ohms in parallel with 0·035 mfd., i.e. Z=368 ohms.

Discussion

From the above results there is no doubt that if the lowest possible body resistance is required, gentle abrasion of the dry skin with glass paper, followed

by application of green soap and then of the electrodes is the most convenient method. Provided the rubbing is gentle and only two or three strokes are used, the skin will return to its normal appearance in a few hours. In our experience there is nothing objectionable in making this a routine procedure, provided that no irritating antiseptics, such as iodine, are applied afterwards. Only one minor difficulty appeared ; it is rather hard to use glass paper on hairy parts, because the hairs roll round under the paper and no abrasion of the skin is made. This could be overcome by removing the hairs before abrasion. It was found that more vigorous glass papering, or scratching, which left a mark taking over a week to disappear, did not give lower values than the more gentle method.

By the use of the procedure recommended above the external resistance (i.e. of the patient) becomes a much smaller fraction of the resistance of the galvanometer, which should then be expected to give a better record of the potentials occurring in the patient's body. Also, when the patient's resistance is low the electrocardiograms obtained should be more standard, as even relatively large alterations of this resistance will then have little effect on the total resistance of the circuit. We have found that in the case of the A.C. bridge the capacitance value (without abrasion) varies from 0·15 to 0·5 mfd., using the same electrodes. It is difficult to predict what would be the effect of this capacitance on the electrocardiogram. The effect on damping of capacitances across the string has been studied by Gildemeister (1922). Here again, however, more standard results would be expected when the capacitance is low, as is the case when the skin is abraded, because the variations in the capacitance then become of small importance. It was also noted that when the skin was abraded the values of R and Z tended to be very steady, whereas without abrasion there was a tendency to drift.

It is interesting to speculate how far the differences which are occasionally found between records taken by string and valve electrocardiographs are dependent on high patient resistance and impedance. There seems to be a tendency to regard records taken by a string galvanometer as standard, in spite of its relatively low resistance. This tendency seems to be based more on tradition than on pure reason. It would be interesting to compare string and valve electrocardiograms in a series of cases taken with the technique described here. We venture to think that with the low patient resistances so obtained a number of the discrepancies would disappear. This question has already had some attention directed to it by Pardee (1929).

Variations in the Quality of the Green Soap.—During the course of these experiments we had occasion to purchase three separate samples of Sapo Mollis B.P. The first sample was soft, bright green in colour, and spread very easily and evenly over the skin surface. The second sample was harder, dark green in colour, very tenacious, and became caked when rubbed on the skin, refusing to spread evenly. The following figures show that this second sample was inferior to the first for our purposes. The values for R were usually over 10,000 ohms, and the average value for Z (11 observations) was 915 ohms, compared with the averages R 2040 ohms and Z 768 ohms for the first sample.

The third sample of Sapo Mollis was comparable in every way with the first, and in obtaining it the following criteria were observed. The green soap must be *fresh* and should be *bright* green in colour, and it should spread as easily on the skin as a good ointment base. It should be kept in an air-tight tin or waxed carton.

The difference in effectiveness was not due to a change in the resistance of the soap. The specific resistance of the second sample (tough soap) was 18·4 ohms per cm. cube ; the value for the third sample (good soap) was 23·9 ohms per cm. cube. It is to be presumed that the lowering of skin resistance with the good soap is due to the fact that it spreads so easily and evenly over the skin.

Summary

Reasons are given for the necessity of having a low limb to limb resistance when obtaining electrocardiograms either by the string galvanometer or by a valve electrocardiograph.

A comparison has been made between four electrolytes, viz. 1 per cent. sodium chloride, soft green soap, Cambridge electrode jelly, and Boston paste (Jenks and Graybiel, 1935).

The arm to arm D.C. resistances (R) and impedances at 300 cycles per second (Z) vary over a wide range for all these electrolytes. From this point of view the best is probably Boston paste, but Cambridge jelly and soft green soap are very little inferior.

Because it is cheap, clean, simple, and a standard pharmacopœial product soft green soap appears to be the most satisfactory. It should be fresh, bright green in colour, and should spread easily over the skin.

Both the Boston paste and the Cambridge jelly contain abrasives. Incorporation of an abrasive in the green soap reduced the average values of resistance and impedance to a moderate extent.

The lowest values of limb to limb resistance (R, 500 ohms ; Z, 400 ohms) were obtained when the abrasion preceded the application of the electrolyte as follows : the dry skin was stroked gently two or three times with fine glass-paper, green soap was then applied and the electrodes were bound on.

We should like to thank Dr. Joseph Knox and Dr. G. W. Tyrrell for advice on certain chemical matters, and Dr. R. G. Lendrum for taking string galvanometer records.

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SIR JAMES MACKENZIE'S HEART

BY

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WITH AN ACCOUNT OF HIS CLINICAL HISTORY BY JAMES ORR, AND NOTES ON THE PATHOLOGICAL HISTOLOGY BY D. F. CAPPELL.

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Received March 9, 1939

The following description of Sir James Mackenzie's heart has been prepared in accordance with his desire, expressed to myself and to other friends, that after his death his heart should be examined to ascertain what information it furnished upon the symptoms that he had experienced. He died in London on January 25, 1925, aged 72. Some weeks before his death he told Dr. John Parkinson that he wished him to make a post-mortem examination. This request was confirmed, after his death, by his brother, Sir William Mackenzie, now Lord Amulree. The examination was performed, some fourteen hours after his death, by Dr. John Parkinson, assisted by Dr. J. W. Linnell. The heart was removed and subsequently sent to me at St. Andrews for further examination. Dr. Parkinson noted that nothing abnormal was found in the pericardium.

In order to correlate the clinical symptoms with the pathological condition, it has been necessary to compile an account of Sir James Mackenzie's illness. This has not been easy for, like so many other doctors, he had not been under the care and observation of a medical man from the commencement of his illness. His own case is referred to both in his book on angina pectoris (Case No. 28) and in that on diseases of the heart, as well as in the Reports of the St. Andrews Institute.

While he was in London, from 1908 to 1918, he mentioned to Sir Thomas Lewis that his anginal history began suddenly. While he was in St. Andrews, from 1918 to 1924, engaged in founding the Institute for Clinical Investigation which bears his name, he was on many occasions examined by Dr. James Orr, and discussed with him his condition. Dr. Orr also saw him during several of the attacks of angina, from which he suffered with increasing severity as the years went on. After his return to London in 1924 he was not under the care of any medical man until very shortly before his death, when he was seen by Dr. Parkinson and Dr. C. M. Anderson.

Dr. Orr, who had seen him during the whole of his stay in St. Andrews, has written the account of the clinical history which follows. My colleague, Professor D. F. Cappell, undertook the histological examination of the blood vessels and heart muscle, and his notes on them are included in the description.

CLINICAL HISTORY AT ST. ANDREWS

The medical life history of Sir James Mackenzie is the story of the onset and gradual progress of angina pectoris from sclerosis of the coronary arteries. He had a mild attack of typhoid fever in 1880 and an occasional attack of renal colic in his later years, but suffered from no other illness.

With the exception of a tendency to extrasystoles commencing at the age of forty, the first evidence of real cardiac involvement was in 1901, at the age of forty-seven. This was a heart attack with irregularity of the pulse, which occurred after running 300–400 yards. In his own description of this attack (Mackenzie, 1925) he notes that he " was conscious of a slight fluttering sensation, but suffered no distress of any kind." The pulse rate during this attack, which lasted two hours, was 90 per minute. A tracing, taken by himself, showed auricular fibrillation. During the next four or five years several attacks of this kind occurred, mostly after a full meal or when walking up a hill ; they lasted from ten minutes to half an hour and never caused any distress or limitation in his powers of walking.

The earliest symptom of limitation of effort was noticed by himself in 1907, and was represented by a slight feeling of constriction, hardly amounting to pain, in the upper part of the chest on severe continued exertion, and which soon ceased with rest. There were long periods when it was not experienced at all. For two years he was conscious of slight pain on effort under certain conditions, such as walking after a full meal or on a cold day. This pain he described as preceded by a sense of tightness or constriction, such as used to pull him up when running a race in boyhood.

In 1908, at the age of 55, Mackenzie experienced his first severe attack of cardiac pain. It occurred at night when resting, and followed a period of dining out at frequent intervals. The pain was across the chest and down the left arm ; it lasted two hours and varied in severity. Mackenzie further notes that in this attack " he could not be still but had to move about." After 10 grains of veronal sleep was obtained, and next day he was quite well and free from pain, though walking in the cold or after a meal still produced discomfort of an anginal type. This gradually became more noticeable, and by 1911 there was definite limitation of effort, though pain could be avoided by careful regulation of effort. From this time until the end of his life a somewhat anomalous symptom was present, to which he often referred, namely, that while a sustained effort produced pain, a sudden effort produced breathlessness without pain.

Mackenzie came to St. Andrews in 1918, and at that time was able to walk

at any pace from his home to the Cottage Hospital without discomfort, a distance of two miles. In 1919, when I first examined him, he was still able to do this and could play a round of golf regularly. The heart was then 1/4 inch external to the mid-clavicular line, the sounds were closed and well spaced, and, except for an occasional extrasystole, the rhythm was regular. Blood pressure was 156/92 mm. At this time he was also affected with intermittent claudication on continuous walking. He had first noticed this ten years previously after a rapid four-mile walk, but in 1919 it was evident after a short half-mile walk. The posterior tibial pulse was well felt on both sides. During the next five years this symptom was much less pronounced owing to the fact that pain in the chest occurred in response to a smaller effort than was necessary to produce claudication.

In 1922 limitation of effort prevented his playing golf, and even walking became difficult though by careful regulation of effort, severe pain was, in the main, avoided. A few very severe attacks occurred, like that in 1908, while resting. The most severe of all, in 1923, happened while he was sitting in his study in the afternoon, and lasted nearly an hour ; it was little influenced by nitroglycerine and was followed by extreme exhaustion. In August 1924 Mackenzie returned to London, and by this time only the gentlest of exercise was possible. Death followed a very severe and prolonged anginal attack in January 1925. As has been already mentioned, Dr. John Parkinson saw him shortly before his death, and has supplied the following note :

" On January 24 and 25, 1925, he suffered severe and prolonged attacks of anginal pain, and Dr. C. M. Anderson was called during the night. At 4.30 a.m. on January 25 he had morphine subcutaneously, gr.$\frac{1}{4}$, and chloroform inhalation for about an hour. It was necessary to repeat both at 8.20 p.m. on that day. At this time the pulse was 100 and regular and there was Cheyne-Stokes breathing. I did not myself see him until 10.30 p.m. that night (January 25), and he was then asleep. About 1 a.m. on January 26 he awoke free from pain and perfectly conscious and composed. He conversed cheerfully with Lady Mackenzie and me for a few minutes and then said he felt sleepy and soon he slept. At 4 a.m. his breathing changed and became irregular with long pauses, and a few minutes later the pulse stopped. There were no indications of pain at the end."

EXAMINATION OF THE HEART

The heart was uniformly enlarged. Its weight was 18 oz. (510 g.) and it measured 14 cm. transversely, 13 cm. vertically and 28·5 cm. in circumference at the base of the ventricles. It should be mentioned that Mackenzie was a tall man of powerful physique, in whom a heart above the average size would be expected.

There was a considerable amount of sub-epicardial fat, especially in the right A-V sulcus, along the right border, and in the anterior interventricular

furrow. The epicardium was smooth and nowhere thickened. The veins on the surface of the heart were distended and more prominent than usual. On the anterior surface, numerous small vessels passed from the inter-ventricular furrow towards the left border, anastomosing with small vessels there, and these in turn with branches of a medium sized vessel on the inferior surface.

The right auricle, was dilated. Its wall was thin and, between the bundles of the pectinate muscles, translucent. The opening of the coronary sinus was large. The crista terminalis and the valve of the inferior vena cava were prominent. The tricuspid orifice and valve were of normal size and showed no pathological changes.

Microscopical Examination.—In longitudinal section the wall measured 7·5 mm. in thickness, of which the outer 6 mm. was chiefly adipose tissue containing a few scattered muscle bundles showing atrophic changes supervening on previous hypertrophy. In the outer fatty layers several small non-medullated nerve bundled were present, together with a few groups of sympathetic nerve cells. In the inner part of the wall the muscle bundles were more closely packed, the individual fibres were hypertrophied, and some showed atrophy and degeneration with increase of fibrous stroma between the fibres.

In transverse section the appearances were of a similar nature and indicated a considerable degree of ischæmic atrophy and fibrosis of some duration. There was no evidence of recent infarction, and foci of inflammatory infiltration were absent throughout the sections.

The right ventricle was large, its muscular wall rather thin, pale in colour and in places almost yellowish. There was no evidence of fibrosis of the wall. At the base of the infundibular portion, where the inner surface was smooth, the muscular coat was 6 mm. in thickness, while about the middle of the cavity, where papillary muscles were present, it measured 16 mm., of which more than half was sub-epicardial fat. The pulmonary valve was normal in structure and competent.

Microscopical examination of the papillary muscles.

(*a*) The sections showed a portion of papillary muscle on transverse section with a central arterial twig accompanied by a small nerve bundle. At one side was an area of adipose tissue separated from the endocardium by thin fibrous layer at one side and by a few muscle bundles at the other. The fibres of the papillary muscle were hypertrophied, but there was no increase of fibrous tissue and no evidence of old or recent infarction.

(*b*) The longitudinal sections of papillary muscle showed essentially similar features : marked infiltration of adipose tissue, hypertrophy of the muscle bundles and, in one group of sections, a mild degree of ischæmic fibrosis towards the attached end of the papillary muscles.

The arterial twigs in the papillary muscle had slightly thickened walls but their lumina were not narrowed.

The left auricle measured 7 cm. in diameter, both transversely and vertically. Its wall was thin and measured only 2·5 to 3 mm. in thickness. The mitral orifice admitted two fingers and the valve was competent. The marginal cusp was

FIG. 1.—Section of the wall of the left ventricle near the apex, showing a recent small hæmorrhagic infarction, involving the deeper part of the muscle wall, covered by a nodular reddish-brown mass of clot, the size of a cherry-stone, projecting into the cavity of the ventricle

short and its surface nodular, especially near the attached margin. It was incompletely divided into three portions. It measured 6 cm. along its base and 17 mm. from the base to the free margin. The aortic cusp was, as is usual, much larger, and measured 24 mm. from its attached to its free margin. It showed no evidence of pathological changes.

The left ventricle was a large and thick walled chamber. The muscular wall, for the most part thick and firm, was 27 mm. in thickness near the base. At the apex, as usual, it was thin, and only 3 mm. in diameter. In colour it was somewhat pale. In its substance were several small whitish patches of fibrous tissue, in size from a pin's head upwards. In the anterior wall, 30 mm. above the apex, there was a patch of fibrous tissue 8 by 3 mm. and another patch of similar structure and size lay in the substance of the posterior wall, about midway between apex and base. At the apex there was a smal lrecent hæmorrhagic infarction involving the deeper part of the muscle wall, covered by a nodular reddish brown mass of clot the size of a cherry stone which projected into the cavity of the ventricle (Fig. 1). Section through this and the adjacent wall showed that the nodular tissue extended into the substance of the muscular wall, which was here reduced to a narrow margin 3 mm. thick.

Microscopical examination.—The section comprised the whole thickness of the ventricular wall. The muscle fibres in the outer layers were greatly hypertrophied and the interstitial tissue was of about normal amount. In the inner half the fibres showed a much greater degree of ischæmic fibrosis and irregularly shaped fibrous scars were numerous, in which muscle fibres in all stages of atrophy were found. The section did not contain any large branch of the coronary arteries and the smaller branches included showed a little thickening of their muscular coats, but no noteworthy intimal change.

The section of the infarction showed a portion of the apex of the left ventricle, the endocardium being partly covered with thrombus both old and recent. The muscle fibres were in general much hypertrophied, but there was a rather severe patchy ischæmic fibrosis which had produced marked thinning of the ventricular wall at the apex. On the internal aspect there was severe subendocardial fibrosis with many muscle fibres undergoing atrophy and degeneration and over this area there was a mass of old thrombus, decolorized in the centre and showing an early stage of organization. The greater part of the thrombus, however, was of recent coralline type and was well preserved, being only loosely attached to the wall. Between the thrombus portions of the columnæ carneæ were seen to be the seat of ischæmic fibrosis with fatty and vacuolar degeneration of the surviving fibres.

The apical myocardium did not show any sharply defined infarctions, but just at the apex there were several patches of more intensely eosinophile fibres whose nuclei appeared to be pyknotic and degenerate. Between these fibres there was a considerable degree of leucocytic infiltration which extended into the overlying epicardial fat. The small blood vessels in the fat were dilated and engorged with blood. None showed any evidence of thrombosis. It is probable that the areas of altered staining reaction and leucocytic infiltration were in a condition of early infarction.

The aorta had been divided 6 to 7 cm. from its root. At the point of division the lumen was cylindrical, measuring 33–34 mm. The ascending aorta showed a bulging to the right side (the bulb of the aorta) by which the

diameter was increased to some 45 mm. The interior of the ascending aorta showed extensive yellow mottling in patches, some separate and some discrete, 3–4 mm. in diameter. Near the root the mottling formed an arborescent pattern. The surface of these mottled areas was slightly raised. In thickness the wall measured 3·5–4 mm., but in places it measured 6 mm. On the posterior wall of the interior of the aorta was a large yellowish raised patch beginning about 35 mm. from the root of the aorta and extending beyond the level at which the vessel had been cut. In this area there was very considerable thickening of subintimal tissue and the tunica intima readily separated off from the other coats. The root of the aorta showed comparatively little pathological change. There were small thin yellow patches of atheroma round the root of the right coronary artery and adjacent to the orifice of the left coronary artery, but the lumen of these vessels was not materially narrowed. Except for the large area mentioned, the wall of the aorta was pliable and showed no general pathological alteration, there being only slight subintimal atheroma.

Section of the patches on the wall showed atheromatous changes of the intimal and subintimal coats. External to the smooth endothelium of the intima was a firm, pale yellow layer some 3 mm. in thickness ; external to this the darker coloured and almost unchanged tunica media. There was little, if any, calcification in the subintimal thickenings.

Microscopical Examination.—The aortic wall was greatly thickened by a large atheromatous patch which measured 1·5 mm. in thickness. External to this the

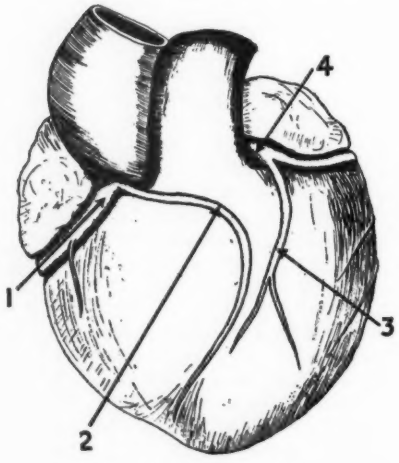

FIG. 2.—Arrangement of the coronary vessels on the anterior surface of heart.

(1) Stem of right coronary artery. (2) Interventricular branch of right coronary artery. (3) Interventricular branch of left coronary artery. (4) Left coronary artery.

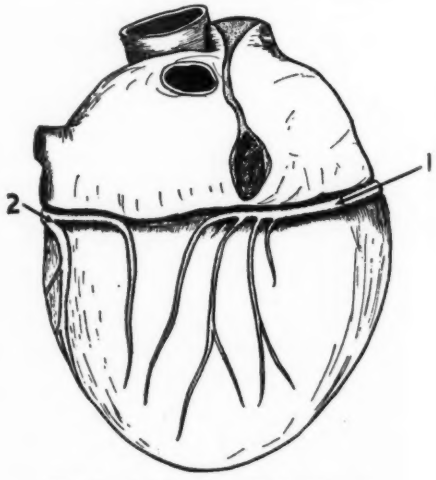

FIG. 3.—Arrangement of the coronary vessels on the inferior surface of heart.

(1) Right coronary artery. (2) Left coronary artery.

medial coat measured 1·15 mm. in thickness. The atheromatous lesion was of the usual type, consisting of degenerate fatty and granular material, with masses of foamy cells and also areas of clefts resulting from fatty crystals. In places the atheromatous lesion involved the innermost part of the media, with foamy cells between the musculo-elastic layers and degenerative changes in the inner elastic laminæ and muscle fibres. The middle coat was a little hypertrophied and in the outer part the tissue elements were comparatively healthy ; inflammatory cellular infiltration was absent and the elastic laminæ were intact.

Coronary arteries.—Both of the arteries and their branches were the seat of advanced and widespread degenerative changes, which had caused thickening of the wall of, especially, the medium-sized and smaller vessels, and diminution of their lumen. The arteries most affected were those in the anterior ventricular furrow, of which there were two, one from each coronary stem. These vessels were so thickened and calcified that their lumen was almost obliterated. A recently occluded vessel was not found as a cause for the infarction mentioned above.

Right coronary artery.—Near its root the external diameter of this vessel was 9 mm. Its wall was greatly thickened and the lumen, oval in outline, measured 2 by 3·6 mm. The thickening involved mainly the subintimal coat and also the tunica media, and the wall was firm and rigid. Section of the wall showed patches of degenerated cheesy material in the centre of the thickened areas, and the changes involved almost the whole circumference of the vessel.

From near the root of the artery a branch, 4 mm. in diameter, passed in the anterior interventricular sulcus to the inferior margin, lying by the side of a slightly larger branch from the stem of the left coronary artery. The two vessels ran side by side in the anterior longitudinal furrow, the left one giving a superficial branch and then entering the muscular coat half-way down, while the right artery ran onwards superficially. The wall of both of these vessels was greatly thickened, and the lumen in each reduced to a minute capillary cleft.

Half an inch from its root the diameter of the right coronary artery was 8 mm. At this point the thickening was less pronounced and the lumen wider. The artery continued as a large vessel and gave off numerous branches ; a small branch in the epicardial fat along the right margin ; a very tortuous branch which ran on the inferior surface an inch from the right margin ; a small vessel to the base of the ventricle ; at the left portion of the coronary sulcus three branches to the inferior surface of the ventricle, arising close to one another and measuring 2–3 mm. in diameter ; finally, the terminal portion of the artery turned downwards in the inferior interventricular sulcus. The distal portion of the artery showed much slighter pathological change, the lumen, though diminished, being distinct.

Histological Examination

(*a*) *Stem of the right coronary artery* (Fig. 4).—The artery was greatly enlarged, the maximum diameter being 7·5 mm., owing to confluent patches of atheroma which surround the lumen and produced irregular narrowing. Adjacent to the lumen there was a thick subendothelial layer of hyaline connective tissue beneath which at one side there was a large crescentic patch of dense calcification, 3·5×2 mm., extending as far as the junction with the media, the muscular layer of which was thinned and atrophied. At the other side of the vessel the intima was fully 3 mm. in thickness and consisted chiefly of degenerate and granular material throughout which there are clefts left by dissolving out of fatty crystals. Foci of calcification were present in this material here and there. Red blood cells had seeped into the degenerate material in places and were seen in well preserved state in the superficial part of the atheromatous lesion. The medial coat of the artery was thin and atrophied. The adventitia had been largely stripped off during dissection. A small arterial twig seen leaving the parent vessel was practically unaffected by atheroma. There was no evidence of thrombosis in this portion.

(*b*) *More distal portion.*—This portion of the vessel measured 5 mm. in greatest diameter and was concentrically thickened, the lumen measuring 2 mm. The thickening was due chiefly to increase of the intima, which consisted of hyaline connective tissue with pronounced patchy granular and fatty degenerative changes in the deepest layers next to the media. These showed the usual cleft-like spaces where fatty crystals had been removed and there were several patches of calcification, the largest measuring 1·25 mm. in diameter. The media showed atrophy of the muscular layers which were reduced to a mere trace over the larger calcified patches. At the junction between media and intima there were, at several places, clusters of wide, thin-walled vessels filled with red cells and around these a mild round-celled infiltration. These appeared to be reactive, newly formed vascular channels, and from them a few thin-walled capillaries extended into the hyalinized layers of the thickened intima. The adventitial coat had been largely stripped off in dissection, but where present showed no evidence of inflammatory reaction. The lumen of the vessel was free from thrombus.

(*c*) *Ventricular branch.*—The vessel was smaller but showed similar though less severe change. There was again widespread atheroma, but the lumen was not so greatly reduced and there was an absence of the calcification so prominent at the higher level. The sections were not quite complete, a portion of the media being missing from one side in all sections. At one side the atheromatous intimal lesion consisted largely of foamy cells with patches of degeneration devoid of cellular structure, and at one point the surface had broken down and a small atheromatous ulcer had formed. This appeared to be very recent, as there were foamy cells mingled with fresh blood corpuscles in the lumen, but there was no evidence of thrombus formation over the damaged area. The tunica media was somewhat atrophied, but there was no noteworthy fibrosis. The adventitia showed no lesion.

(*d*) *Interventricular branch* (Fig. 5).—The artery was thickened, measuring 4×3 mm., and the lumen was eccentric and was reduced to a mere crescentic slit 1×0·3 mm. Opposite the convexity the intima was occupied by two large patches of very degenerate atheroma showing abundant fatty clefts and granular material. These patches had become confluent and both were surmounted by a mass of hyaline connective tissue. The larger patch showed much calcification of its outer portion next to the media. Opposite the convexity of the lumen the intima was thickened by multiple layers of hyaline stroma, without fatty degeneration in the deeper layers, and around the lumen the connective tissue was more loose and cellular and its arrangement suggested a recent formation indicative of arterial closure such as occurs in endarteritis from diminished blood flow.

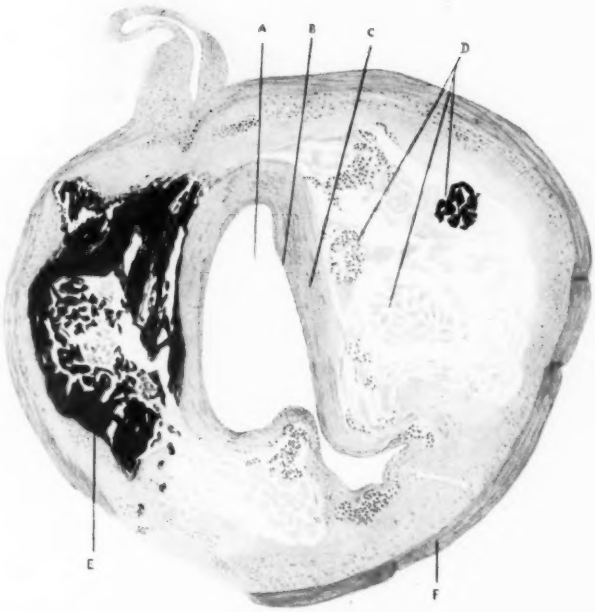

FIG. 4.—Section of the stem of the right coronary artery, showing the lumen irregularly narrowed by thickening of the sub-endothelial and middle layers, and patches of degeneration and calcification.
(A) Lumen. (B) Endothelial tunic. (C) Sub-endothelial tunic. (D) Patches of degeneration and calcification in middle tunic. (E) Large calcified area. (F) Adventitial tunic.

The media was much thinned and atrophied and overlying the larger calcified intimal patch there was complete disappearance of the muscular layer. A few wide, thin-walled vessels of newly-formed type were seen between the media and intima

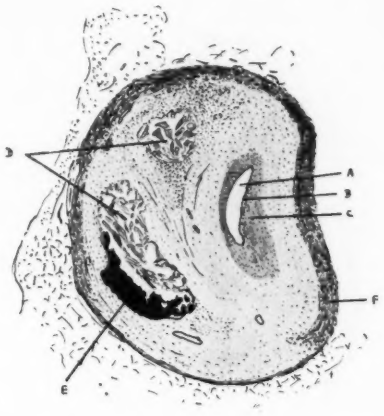

FIG. 5.—Section of interventricular branch of right coronary artery.
(A) Lumen. (B) Endothelial tunic. (C) Sub-endothelial tunic. (D) Patches of degeneration. (E) Calcified patch. (F) Adventitial tunic.

surrounded by round cells and a few foamy macrophages. In the adventitial coat there were several patches of round-cell infiltration, chiefly lymphocytes ; plasma cells did not appear to be present.

The left coronary artery was smaller than the right, and its wall was less affected by pathological change. The external diameter at the root was 6 mm. and the wall not more than 1 mm. thick. It gave off a large branch already mentioned to the anterior interventricular furrow ; the wall of this branch was more affected pathologically than the stem of the artery, there being marked intimal thickening in patches near the root, while an inch or two distally the thickening was even more pronounced, involving the whole wall and reducing the lumen to an extremely small size. The left coronary artery gave a large branch to the left margin of the heart. The wall of this branch too was distinctly thickened, and in the more distal portion so thickened as to reduce the lumen to the smallest dimensions.

(*a*) *Marginal branch* (Fig. 6).—The section showed a portion of cardiac muscle and one large artery and two small branches, the largest vessel measuring 3 mm. in diameter. The lumen was reduced to an eccentric elongated slit $1{\cdot}6 \times 0{\cdot}065$ mm. in diameter. At one side the intima was occupied by a large patch of degenerate atheroma consisting of granular material and clefts of fatty crystals with much calcification in the deeper layers. External to this area the media was almost totally destroyed and there was an abundant formation of new capillary vessels widely dilated and thin walled, between the deeper part of the intima and the media and at one point replacing the muscular wall completely. This newly-formed vascular tissue was

filled with round cells and macrophages, many of which were packed with dark brownish pigment which gave the Prussian blue reaction for iron. Similar cells were present in abundance in the adventitial coat overlying the lesion. The appearances suggested that there had been an interstitial hæmorrhage which had become organized

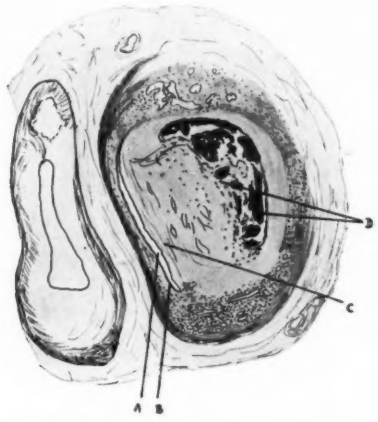

FIG. 6.—Section of marginal branch of left coronary artery, showing the diminished slit-like lumen and a large patch of degenerate atheroma, destruction of the media, and newly-formed vascular tissue replacing the muscular wall. Two smaller vessels show moderate sub-intimal thickening but absence of atheromatous disease.

(A) Lumen. (B) Endothelial tunic. (C) Sub-endothelial tunic. (D) Degenerated and calcified patches in middle tunic.

and repaired. The two smaller arterial branches showed a moderate degree of subendothelial intimal thickening, with musculo-elastic hyperplasia, but atheromatous disease was absent.

(*b*) *The interventricular branch* measured 3·2 mm. in diameter, the lumen, eccentric and almost circular, measuring 1·0 mm. The thickening was again due to severe atheroma, two patches showing marked degeneration and calcification being confluent, while less pronounced atheromatous deposits were also present on the opposite wall. The media was much thinned over the calcified patches, being almost devoid of muscular tissue.

There was also a minor degree of new capillary formation between media and intima and in several places thin walled capillaries had penetrated some distance into the degenerate intima and could be seen between the degenerate fatty patches and the subendothelial hyaline layer, which was, however, completely avascular.

The adventitial coat showed only a single small focus of round-cell infiltration and was devoid of pigment bearing macrophages.

Summary of Condition of Vessels

Both coronary vessels and their branches showed extensive and far-advanced sclerosis in the form of patchy thickenings of the wall, which in some instances diminished and practically obliterated the lumen.

THE CONDITION OF THE HEART IN RELATION TO THE SYMPTOMS

(1) The first signs of heart impairment occurred in 1908, seventeen years before his death, when he experienced a sharp attack of severe pain, which with our present knowledge would be diagnosed as due to a coronary thrombosis. There is evidence in the heart to confirm this view, for the patch of fibrosis near the apex corresponds to the structural damage which would be caused by such an attack.

Sir Thomas Lewis, who was good enough to send me his opinion after examining the heart, wrote to me as follows :

" Grant and I examined the heart very closely and we are agreed that there are amply sufficient old-standing changes at the apex of the heart to account for the first attack of pain described in his case notes. That attack of pain is strongly suggestive of coronary thrombosis, and the fibrosis at the apex is distributed in a way that also suggests thrombotic obstruction of an apical branch."

(2) The severe atheroma of the coronary arteries and their branches, with diminution of the lumen, affords ample cause for the occurrence of attacks of cardiac pain. Both of the arteries were affected and the anterior interventricular branch of each was greatly narrowed.

(3) There were numerous small patches of cicatrization in the substance of the muscular wall of the left ventricle. These patches though smaller were of the same nature as the larger fibrous patch at the apex, which was due to thrombosis of an apical branch. Other arteries to the left ventricle were profoundly altered and their lumen narrowed. This has been shown for example in the marginal artery of the left ventricle. There would therefore appear to have been numerous small thromboses at different times, each of which would be accompanied by symptoms similar to those experienced at the first attack. Several such attacks are recorded and the similarity is brought out in the case history. It is noted, for example, that on many occasions the attacks came on during rest and were quite unrelated to effort.

(4) The presence of numerous small blood vessels on the surface of the heart points to there having been an opening up of small vessels and the establishment of at least a partial anastomotic pathway for the supply of blood to the areas most severely impaired by the attacks of thrombosis. In this connection it may be remarked that during the last few months of his life between August 1924 and January 1925, Sir James's condition showed slight improvement. I found, for example, that not only could he walk for some distance down Exhibition Road from his home in Albert Hall Mansions, but he was able to walk up that road without distress, though at a slow pace. This improvement doubtless was due to a slight improvement, by anastomosis, in the arterial supply to the heart.

(5) The terminal severe attack of pain and cardiac impairment was associated with the occurrence of the recent infarction found at the apex of the left ventricle.

(6) There was no evidence of any impairment in the valves or in the genetic

system of the heart. The impairment was entirely in the muscular wall, brought about by the atheromatous disease of the arteries.

We have to thank Miss M. H. Kidston for preparing illustrations 1–6.

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CARDIAC MYXOMA

A CLINICAL AND PATHOLOGICAL STUDY

BY

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Received April 12, 1939

We wish to place on record this case of so-called cardiac myxoma because it appears that only rarely do descriptions of this interesting lesion appear in British publications. We have found only one British reference during the last nine years, the case of Gilchrist and Miller (1936) which will be discussed later in this paper ; on the other hand, numerous references have appeared during the last few years in America and Germany. The lesion is a rare one, much less common than the appearance of secondary neoplasm. The latter were found by Welch (1931) in 0·22 per cent. of autopsies, and Ward (1934) reports a corresponding figure of 0·3 per cent., whereas Lymburner (1934) states that primary neoplasms of the heart were found in 0·05 per cent. of autopsies, of this number 75 per cent. were innocent and the majority of innocent tumours were myxomas.

Description of the Case

A woman aged 60 was admitted for the first time to the City General Hospital, Leicester, on March 4, 1938, with the diagnosis of diabetes mellitus and bronchitis. She had previously complained of rheumatic pains in the shoulders and since 1925 she had had various attacks of epigastric pain and vomiting. More recently it had been known that her blood pressure was above the normal. During her stay in hospital her diabetic condition was readily stabilized, nothing abnormal was discovered in her cardiovascular system except slight hypertension, B. P. 170/90 mm., and she was discharged after fifteen days.

Almost immediately after returning home she began to suffer from fainting attacks, but on no occasion was she seen by her medical attendant whilst in an attack. Præcordial pain also occurred and was associated with marked dyspnœa and some cough. Præcordial pain and dyspnœa now continued until December 1938, when diarrhœa started. This symptom became so pronounced that the patient was readmitted to hospital on January 14, 1939, for investi-

gation. No abdominal lesion could be found to account for this symptom and no abnormal physical signs were found in the heart other than slight left ventricular hypertrophy. Her diabetes had remained controlled and she appeared to be in satisfactory health until January 18, when for the first time in hospital there was a complaint of faintness and dizziness which was considered to be a mild attack of hypoglycæmia. A similar attack occurred five days later, and this responded immediately to a hypodermic injection of adrenalin. On the evening of January 28 she had a very severe attack without any previous warning, and when seen she was pulseless and was thought by the sister of the ward to be dead. An injection of 15 minims of adrenalin was given into the left ventricle and 3 c.c. of coramine were injected intravenously. Within two minutes the pulse could be felt at the wrist and the patient recovered consciousness and began to talk.

On auscultation of the heart it was found to be fibrillating and it continued to fibrillate for about 3 minutes before normal rhythm was resumed. The patient appeared quite comfortable for an hour, then, again, without warning, she collapsed ; 15 minims of adrenalin were given into the heart and again the patient, who had for a second time been pulseless, recovered, became a good pink colour and was able to talk. She remained in a satisfactory condition and appeared to go to sleep naturally. About three-quarters of an hour later she slept normally for forty minutes, and then she died suddenly in her sleep. The provisional diagnosis was coronary thrombosis.

Post-mortem Findings (abstract only)

Diagnosis : Acute heart failure, tumour of the left auricle, hyperpiesis.

There was no excess of pericardial fluid. Some hypertrophy of the left ventricle was present with well marked atheroma of the aorta ; but the coronary vessels were excellent and the probe passed readily along them without finding any obstruction. No alteration in the size of any of the valve apertures was found, and all the valve cusps were thin and showed no evidence of previous infection.

When palpating the mitral valve a fairly firm tumour could be felt almost filling the left auricle. On approaching the left auricle from behind, this tumour could be more readily seen (Fig. 1). It was attached to the inter-auricular septum by a pedicle 23 mm. long and 16 mm. broad, the lower point of this pedicle being attached 8 mm. above the attachment of the mitral cusps. The tumour itself was roughly spherical, with a diameter of 40 mm. The length of the pedicle allowed the tumour to be pushed into the orifice of the mitral valve (Fig. 2) and also to fall over the openings of the pulmonary veins. In appearance the tumour was shiny, and there were many small polypi on the surface. It was white in colour save where hæmorrhage beneath the surface was shining through. It was peculiar in consistency, being somewhat rubbery or elastic. On section the tumour was yellow in colour and homogeneous, with several areas of recent hæmorrhage. There was no evidence of scarring

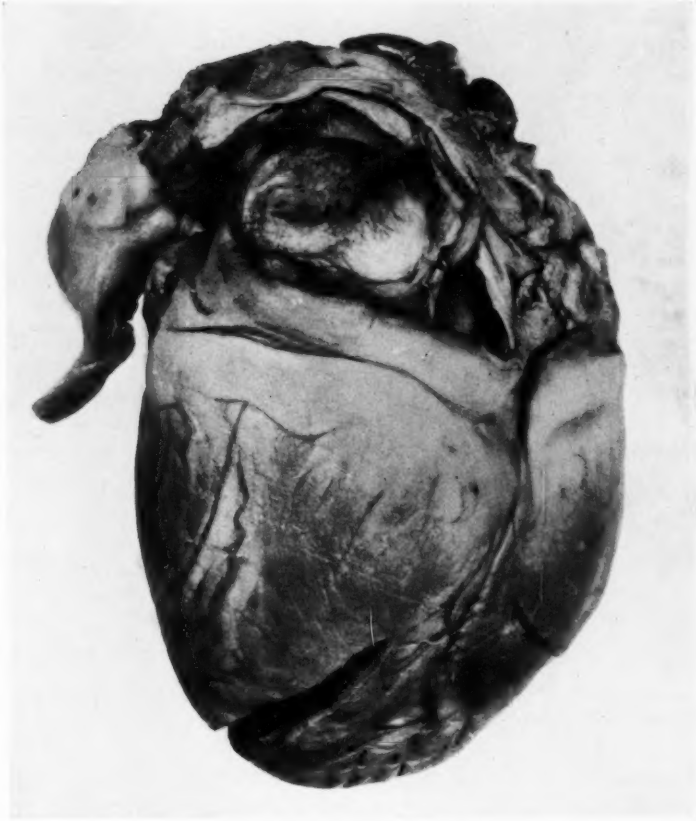

FIG. 1.—Posterior aspect of heart showing myxoma lying in the left auricle ; it is attached to the interauricular septum by a pedicle.

or contracture. (There was considerable shrinking on preservation, and this shows in the plate.)

The lungs showed congestion throughout, this being somewhat more marked at the bases, and there was considerable emphysema. The liver was slightly enlarged and was also congested. The kidneys were smaller than normal, with a very rough granular surface. On section there was increase of pelvic fat and decrease in the size of the cortical layer. The intercortical vessels stood out prominently.

Histological sections were prepared from the base of the tumour and from its free surface. These were stained by hæmatoxylin and eosin, by Van Gieson's stain, by mucicarmine, and by thionin. The tumour appeared lined by a single layer of endothelial cells under which was a thin layer of fibrous tissue. Immediately beneath this layer were masses of inflammatory cells and new

FIG. 2.—Photograph of heart before fixation, showing smooth and shiny tumour projecting through mitral orifice.

blood vessels or groups of endothelial cells which represented new capillaries awaiting canaliculization. Large masses of blood pigment were present, probably hæmosiderin, but little intercellular pigment could be found. Deeper within the section the tumour proper was found. This consisted of a finely fibrillar matrix, cells being relatively scanty. The matrix stained faintly blue with hæmatoxylin, but fairly deeply with mucicarmine and thionin. The cells were large with a vesicular nucleus, and in many cases they showed bipolar or unipolar projections.

Within the tumour proper groups of endothelial cells and capillaries with a single cell lining were found and blood pigment masses were still present, but were less marked. The myxoma cells tended to be arranged around these new blood vessels. The large areas of hæmorrhage were mainly confined to the sub-endocardial region, but deeply within the tumour there were small groups of free red cells. A small amount of elastic tissue was found throughout the sections examined. The picture was therefore one of a myxoma, the number of new blood vessels present hardly justifying the term angiomyxoma.

Clinical Features

No one has yet reported the successful diagnosis of a primary innocent cardiac neoplasm during life. Pavlowsky (1919) made a diagnosis of primary sarcoma of the left auricle, but at the autopsy it was discovered that the tumour was on the right side. A primary malignant tumour, an invasive tumour of a sarcomatous type, was diagnosed by Shelburne (1935) in a case of a male aged 24 with a large blood-stained pericardial effusion.

In many of the reported cases, however, the diagnosis was suggested by

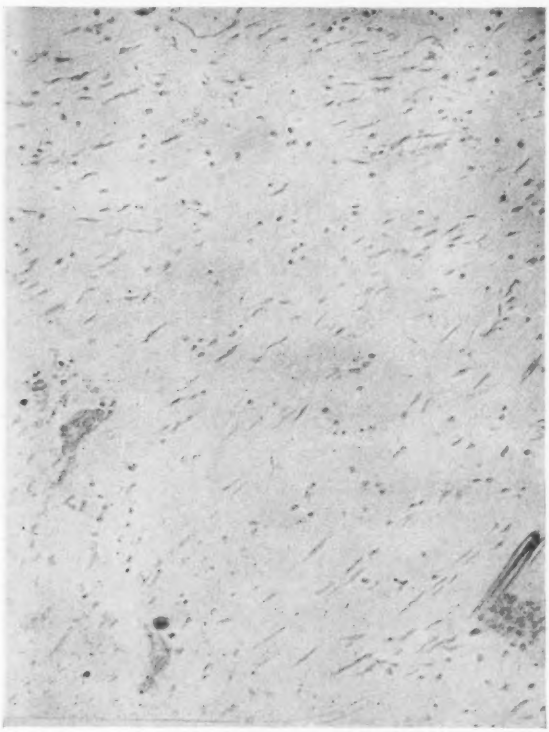

Fig. 3.—Section of cardiac myxoma (×100), showing fibrillar matrix and elongated cells.

certain points in the history, the physical signs, or in the reaction of the patient to treatment, and so it may be of interest to consider a few of the clinical pictures which have been described as follows.

(1) *Mitral Stenosis with Congestive Heart Failure.*

The picture of mitral stenosis with congestive heart failure is the commonest one to be described. A typical case is described by Jensen (1934) in a woman aged 32 who had complained of shortness of breath and œdema for two months,

and clinically showed ascites and a heart condition typical of mitral stenosis. There are three important points which appear, however.

(*a*) The cardiac signs and especially the murmur vary from time to time. Thus in the case described by Bien and Ch'in (1936) a rough high-pitched systolic murmur present all over the præcordium, but loudest at the apex, was heard when the patient was in hospital but whilst an out-patient a rumbling mid-diastolic murmur or a third heart

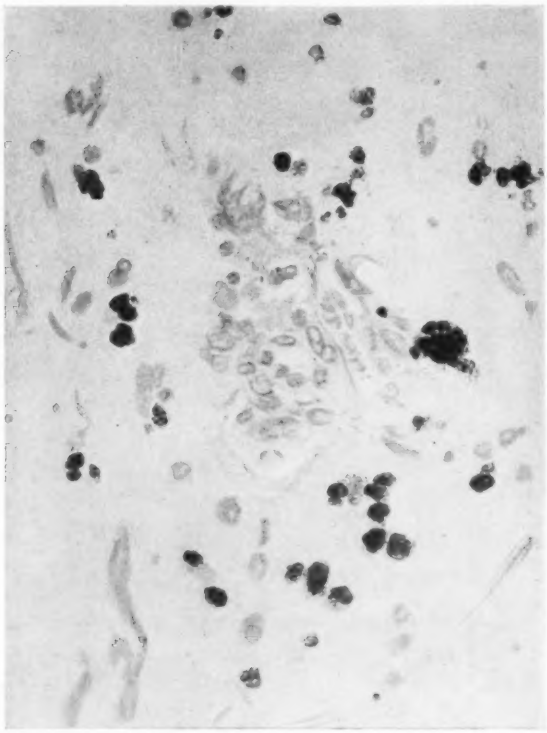

FIG. 4.—Section of cardiac myxoma (×450), showing cells arranged near blood vessels ; large amount of pigment.

sound prolonged into a diastolic murmur was found at the apex. Gilchrist and Miller point out that the obstruction of an auriculo-ventricular orifice by a tumour retards the blood flow and narrows the stream and this fictitiously produces the ausculatory signs of a valvular stenosis.

It is obvious that in certain positions the tumour will fall away from the valve orifice, with the result that the blood flow is not impeded and the heart sounds change in character.

(*b*) These patients rarely give a previous history of antecedent diseases, such as rheumatic fever, chorea, growing pains or recurrent sore throats, which might have lead up to a mitral stenosis.

(*c*) The history of cardiac debility is usually a short one.

(2) *Fainting Attacks and Loss of Consciousness with the Patient Erect*

The case described by Houck and Bennett (1929–1930) demonstrates well this group of cases. The patient was a female, aged 44, who had always enjoyed the best of health and denied all previous history of rheumatism. She was an athletic type and indulged in a considerable amount of swimming. Suddenly, six weeks before admission to hospital, she had a fainting attack as she stood up after leaving the water. After this, fainting attacks recurred at weekly intervals, always whilst the patient was erect. There followed in rapid succession dyspnœa with œdema of the ankles, cyanosis and orthopnœa. On admission to hospital, presystolic and systolic murmurs at the apex and a moderate degree of enlargement of the heart were found. She died suddenly in her sleep during the first night in hospital. At the autopsy a tumour was found in the left auricle which fitted snugly into the mitral orifice. It seems clear that in this group of cases the symptoms depend upon the tumour completely blocking the mitral orifice for a very short time whilst the patient is erect. They depend upon the tumour having a sufficiently long pedicle to allow some movement.

Another case of this kind is described by Gorlitzer (1934). Here a woman was admitted to hospital unconscious with twitching in all the extremities and with preserved reflexes. She had had several previous attacks of an " hysterical " type. At autopsy a myxoma of the left auricle was found with emboli in the left anterior cerebral artery, both middle cerebral arteries and the left posterior cerebral artery.

(3) *Sudden and Unexpected Death*

This group of cases really consists of the final stages of the ones previously described, although there is often no previous history of illness leading up to the final attack. Here the tumour probably does not fall back from the mitral orifice and death ensues. Lymburner's case (1934) was admitted to hospital for the treatment of septicæmia which was the result of a self-induced abortion, and she died suddenly. There were no abnormal clinical features found in the heart. In Houck and Bennett's case previously described and also in our case death took place quietly during sleep.

(4) *Relentless Progress of Heart Failure in spite of Adequate Rest and Digitilization*

We have already mentioned the case described by Bien and Ch'in, since it demonstrated the point of varying heart murmurs with the position of the

patient, and it is also an excellent example of this type of case. The patient was a male aged 59 when first admitted to hospital in 1934 complaining of shortness of breath which had been present for three weeks. During a stay in hospital of one month he made some improvement and was discharged on a maintenance dose of 0·1 g. of digitalis daily and was instructed to rest at home. This he did. During the following year the cardiac reserve became slowly reduced, so that from being able to walk two-thirds of a mile he could now walk less than a hundred steps, and in January 1935 signs of congestion were found and the patient was re-admitted to hospital. Thus although resting and receiving adequate digitalis and although he had been seen frequently at the cardiological clinic, the lesion first noted in January 1934 slowly progressed during the year until death took place in February 1935. This progress of symptoms is probably dependent upon the slow growth of the tumour ; with more rapid onset or with more rapid retrogression of health dependent upon rapid increase in size such as would follow hæmorrhage into its substance.

(5) *Abnormal Radiological Shadows.*

The enlargement of the left auricle caused by the presence of a large tumour will sometimes produce alterations in the radiological contour of the heart. Bennett and Konigsberg (1938) describe a case, admitted to hospital with a pelvic abscess, who died whilst under an anæsthetic for its treatment. A skiagram showed a large bulge in the region of the pulmonary conus which was considered to be due to congenital abnormality. There was a myxoma in the left auricle. The tumour described by Gilchrist and Miller produced a projection into the posterior mediastinum together with marked enlargement of the heart both to the right and to the left.

(6) *Cardiac Irregularities*

Cardiac myxomas rarely produce irregularities of the pulse. This is readily understood, because as innocent tumours they do not interfere with the conducting mechanism. It is comparatively rare for even extensive involvement of the myocardium with secondary deposits from carcinoma or sarcoma to produce obvious changes in the electrocardiogram. Paroxysmal auricular tachycardia is described by Gilchrist and Miller in a male aged 57 who had complained of præcordial pain for two and a half months. These attacks of pain were brought on by lying flat in bed and were relieved by sitting up. At the height of an attack he "fell away in a trance." Each attack lasted from 10 to 15 minutes. The first diagnosis considered was an anxiety neurosis, but the presence of slight cyanosis and dyspnœa suggested an organic cause for the symptoms. The electrocardiogram showed short runs of auricular paroxysmal tachycardia and numerous auricular extrasystoles intermingling with normal rhythm. These attacks of paroxysmal tachycardia were reduced in

frequency under digitalis therapy, although whilst in hospital right-sided heart failure developed which did not respond to treatment.

(7) *Paroxysmal Dyspnœa*

If the tumour interferes with the orifices of the pulmonary veins instead of with the mitral orifice it will cause sudden back pressure in the pulmonary circulation and thus give rise to pulmonary œdema and dyspnœa. It has frequently been noted that in cases of heart failure due to the presence of a tumour in the left auricle the breathlessness is out of all proportion to the degree of decompensation. Bien and Ch'in say that their patient was suddenly awakened at midnight with a sense of suffocation and had profuse perspiration and palpitations only relieved by expectorating large quantities of frothy sputum. Gilchrist and Miller also describe attacks of paroxysmal nocturnal dyspnœa. Ernstene and Lawrence (1936) report a case, not of myxoma but of an occluding thrombus in the left auricle, in which for several months there had been paroxysms of breathlessness which caused the patient to sit up in bed, when he promptly lost consciousness. Each attack lasted for less than fifteen minutes.

After considering the groups of cases described above, we would suggest that no particular symptom or sign can be taken as diagnostic of an intracavitary tumour of the heart, save perhaps the rare abnormal skiagram; but that, if in any patient the history, the physical signs, and the subjective symptoms do not readily fall together into a complete picture, then the presence of such a tumour should be considered. The case can then be reassessed with this diagnosis in view. Especially might this be true in cases of mitral stenosis who strongly deny all antecedent illness and in whom the cardiac disability is an exceedingly short one.

PATHOLOGY

Although at least 100 descriptions of cardiac myxomas have been published the majority of reported cases are not accepted by all pathologists. Writing in 1922 Husten said that, of the 71 reported cases he discussed, only 9 were true myxomas, all the others being thrombi. On the other hand Ribbert (1924) disagrees with this view and considers that the majority at least of the reported cases are true tumours. Bacaloglu *et al.* (1933), call these tumours " thrombus myxoides " and say that " les myxomes du cœur sont a l'envers de la conception classique des tumeurs des plus rares," and Clerc *et al.* (1937) say that between the true myxomatous or myxosarcomatous tumours and organized thrombi all intermediate forms are possible.

The possible origin of these tumours may be listed :

(1) They are true myxomatous tumours arising, as Ribbert suggests, from myxomatous rests in the region of the fossa ovalis in the interauricular septum.

(2) They are thrombi undergoing myxomatous degeneration.

(3) They are œdematous thrombi, the matrix not being true myxomatous tissue but fibrin swollen by œdema fluid.

(4) They represent myxomatous degeneration in a fibroma.

The main argument lies, it seems to us, between the first two of these possible origins. Are these true tumours or are they thrombi undergoing myxomatous degeneration ? The present view seems to be that they are true tumours. Thus Yater (1931) says : " It seems to me that the argument concerning the nature of these myxomatous masses is all in favour of their neoplastic origin," and Ewing (1928) says " Whilst many of the larger tumours may be difficult to identify it seems unlikely that a simple organizing blood clot can reproduce the positive features of the true myxomas. Hence the great majority of the reported cases of cardiac myxoma are probably genuine."

The presence of small myxomas on the heart valves is not disputed, and cases have been reported by Jaleski (1934) and by Abrahamer (1931), but the origin of the large masses found in the auricle more often on the left than on the right is a debated question. The arguments in favour of these masses being true neoplasms are

(1) Myxomas are always found in the auricles, whereas thrombi are more common in the ventricles. They arise near the fossa ovalis where it is known that myxomatous rests may occur.

(2) There is no previous history in the majority of cases which would lead to stasis in the heart chambers and so allow thrombi to form. Samuel Wilks (1889) very beautifully describes the formation of antemortem thrombi or " polypi " in the dilated chambers of the heart due to the stagnation of blood in the recesses of the columnæ, especially in the left ventricle and the right auricle. He stresses that there must be stagnation to allow thrombus formation.

(3) Myxomas are uniform throughout except where there is hæmorrhage ; there is no evidence of the lamination found in the more common antemortem thrombus.

(4) Microscopically, myxoma shows a poverty of cells, but those present are characteristically spindle or star shaped cells with processes anastomosing or disappearing into the matrix. They may be scattered throughout the tumour or be arranged round the blood vessels or underneath the capsule if the tumour shows peripheral growth. The characteristic cells will not, of course, be found in a thrombus. Elastic tissue may be found in either case. The blood vessels of a tumour are arranged in a uniform manner throughout the neoplasm, and in a thrombus they tend to be scanty deep within the mass.

(5) A thrombus tends to retract and will show scarring, whilst a neoplasm may be smooth, villous, papillomatous or polypoid.

(6) Chemically the presence of mucin cannot be used as an argument either way, since mucin may be found in an undoubted thrombus. The blood pigment in a myxoma is hæmosiderin throughout, whereas in a thrombus the peripheral

pigment is hæmosiderin and the pigment at the centre is the iron-free hæmatoidin.

It is unlikely that these neoplasms are fibromas undergoing myxomatous degeneration because :

(1) They are the commonest primary tumour of the heart, whereas Yater says that only 25 cases of fibroma had been reported up to 1931. The fibromas are never larger than a cherry and in the majority of cases they were placed on the heart valves.

(2) Myxomatous degeneration in an innocent tumour is usually looked upon as a prelude to malignant change and myxosarcomas are exceedingly rare. If all myxomas were an intermediate stage between an innocent neoplasm and a malignant one we should expect obvious primary malignant tumours of the heart to be more frequent than they appear to be in the literature.

Our case answers as far as possible the criteria laid down for the diagnosis of a cardiac myxoma. The tumour was totally unlike any thrombus we have ever seen in a heart, and we believe it to be a true neoplasm.

Summary

(1) The clinical features and postmortem findings in a case of cardiac myxoma are described.

(2) The symptoms and signs in reported cases of cardiac myxoma are reviewed. Obstruction of the mitral orifice by the tumour may produce murmurs like those of mitral stenosis, or may cause fainting attacks related to posture or sudden and unexpected death. Obstruction of the pulmonary veins may cause paroxysmal dyspnœa.

(3) The pathology of cardiac myxoma is discussed and the various views as to their origin are mentioned. Reasons are given for regarding them as true myxomatous tumours rather than as thrombi or fibromas which have degenerated.

We wish to thank Dr. E. C. Hadley, Medical Superintendent of the City General Hospital, Leicester, for his permission to publish this case and the Librarians of the Royal Society of Medicine and the British Medical Association for much help with the bibliography.

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STANDARDIZATION OF METHODS OF MEASURING THE ARTERIAL BLOOD PRESSURE

A JOINT REPORT OF THE COMMITTEES APPOINTED BY THE CARDIAC SOCIETY OF GREAT BRITAIN AND IRELAND AND THE AMERICAN HEART ASSOCIATION.

EDITORIAL

The genesis of the joint report that follows may be explained shortly. In September 1938 the American Heart Association appointed a committee to draw up recommendations for a standard technique for taking arterial blood pressure, and asked the Cardiac Society of Great Britain and Ireland if they would like to appoint a similar committee, which should if possible issue a joint report with the American Committee. The Council of the Cardiac Society approved of this course and appointed a Committee for the purpose.

The reader may feel that such recommendations are not needed and that everyone knows how to take the blood pressure and does it in the same way. The committee have learnt that this is not the case and that many physicians differ in small points of technique, often without realizing that their custom is not universally accepted.

The British Committee met on November 19 and had before them the results of various preliminary enquiries and the excellent short recommendations put forward by a committee of the Assurance Medical Society in May 1931 and published in their journal. The British Committee drew up some recommendations which were discussed with many members of the Council and with other physicians and physiologists. At a second meeting on January 21, 1939, these were put into final shape and were sent to America early in February.

The recommendations and report of the American committee were received about this time, and it was obvious there was a good deal of common ground, but a few outstanding differences. A composite report was drawn up incorporating these agreements and differences, and this has since been the basis for discussion in both countries. This was then brought before the Council of the Cardiac Society, who authorized their committee to publish an agreed draft within the compass of these recommendations.

The British and American committees have both accepted many suggestions where they thought the other had made useful additions or had expressed the

recommendations more clearly ; both, however, have retained to some extent their own phraseology where they thought this more appropriate to their country and have set forth with different emphasis the three remaining points in which agreement was not reached. Two of these three are simple—the British committee expressing a preference for the mercurial manometer as less likely to get out of order, and expressing no choice as to whether the patient is lying down or sitting provided he is comfortable ; the American committee preferring that he should be seated, but expressing no preference between the mercurial and aneroid instruments, provided they are in good condition.

The third more important difference is in the method of recording the diastolic pressure. Both committees agree that the point where the loud, clear sounds change abruptly to the dull and muffled sounds should be recorded. The British committee think this is the only point that should be recorded and that it can nearly always be detected accurately, though at times only with difficulty. The American committee, influenced perhaps by this difficulty, recommend that the point where the sounds disappear should also be recorded.

Apart from these three differences, which are dealt with in the report, and the phraseology, the reports and recommendations were in substantial agreement, and it has been agreed, therefore, that they should be published in each country over the joint signatures of both committees.

MEMBERS OF THE COMMITTEE FOR THE STANDARDIZATION OF BLOOD PRESSURE READINGS

Appointed by the Cardiac Society of Great Britain and Ireland

Dr. Crighton Bramwell, Manchester, England
Dr. Maurice Campbell, London, England
Dr. T. F. Cotton, London, England
Dr. William Evans, London, England
Dr. A. R. Gilchrist, Edinburgh, Scotland
Dr. John Hay, Liverpool, England.

Appointed by the American Heart Association

Dr. M. H. Barker, Chicago, Illinois
Dr. Joseph Erlanger, St. Louis, Missouri
Dr. Jonathan Meakins, Montreal, Canada
Dr. Ralph Schneider, New York City
Dr. S. B. Scholz, Jr., Philadelphia, Pa.
Dr. Harry Ungerleider, New York City
Dr. Paul White, Boston, Mass.
Dr. Carl Wiggers, Cleveland, Ohio
Dr. Irving Wright, New York City, Chairman.

JOINT REPORT ON THE METHOD OF MEASURING ARTERIAL BLOOD PRESSURE

INTRODUCTION

It has long been realized by many teachers and practitioners of medicine that the wide variations in blood pressure records of a single subject were due not only to changes in the pressure from time to time under different conditions, but also to the different methods used by the observers. The interpretation of the sounds heard on auscultation is an important cause of divergent readings. A recent survey of Wright and others (*American Heart Journal*, **16,** 469, 1938) revealed a serious lack of agreement as to the correct technique for taking and interpreting the blood pressure. Similar uncertainty was found among insurance companies as to what they should require of their examiners in this regard. Experiments with multi-aural stethoscopes showed that recent years have brought little if any improvement, as the discrepancy among the recently qualified was as great as among their seniors.

The Committees for the standardization of methods of measuring arterial blood pressure appointed by the American Heart Association and by the Cardiac Society of Great Britain and Ireland have tried to bring about a crystallization of the best available thought on this subject. If feasible, the Committees were asked to make joint recommendations which might be accepted as a standard for practising physicians, medical teachers, and insurance companies.

After a careful study of the material available from many sources and after much discussion the Committees jointly recommend the following procedure as the standard method for taking and recording blood pressure readings in man. Some of these recommendations are dealt with in more detail in the explanatory notes. The British and American Committees have decided to publish over their joint signatures reports which differ slightly in wording and phraseology. In the few instances where there was any difference of opinion, the views of both Committees have been included in each report.

RECOMMENDATIONS

1. *The instrument*

The equipment to be used for measuring arterial blood pressure, whether of the mercurial or of the aneroid type, must be in good condition and requires to be calibrated at frequent intervals against a standard mercurial manometer. The British Committee think that the mercurial type is the most dependable. The proper care of these instruments and the importance of a standard armlet are dealt with in the explanatory notes that follow.

2. *Position of the patient*

The patient should be allowed time to recover from any recent exercise or excitement. He must be comfortable and may be either lying or sitting. The American Committee recommend that he should be sitting and that, if not, a special note should be made.

The arm, relaxed and comfortably supported at the patient's side, must be laid bare to the shoulder to avoid any constriction by a rolled up sleeve and to facilitate proper application of the armlet.

3. *Application of the cuff*

The cuff must be of standard size, with a rubber bag at least 12 cm. wide. The cuff, completely deflated, should be applied with the middle of the rubber bag over the inner side of the arm, and its lower edge one inch above the bend of the elbow. It should fit closely and evenly round the arm to ensure against bulging at the sides when it is inflated.

4. *Determination of the systolic pressure by palpation*

A preliminary approximate reading of the systolic pressure should be taken by palpation as a check on auscultation ; the pressure in the armlet should be raised quickly in steps of 10 mm. until the radial pulse ceases, and then allowed to fall rapidly.

5. *The application of the stethoscope*

The brachial artery should be located by palpation, and the stethoscope applied lightly and accurately over it, just below but not in contact with the cuff. The hand may be pronated or supinated according to the position yielding the stronger brachial pulse.

6. *Determination of the systolic pressure by auscultation*

After inflating the cuff quickly to a pressure about 30 mm. above the level of the systolic pressure as found by palpation, auscultation should be conducted during slow deflation.

The systolic pressure is the highest level at which successive sounds are heard.

7. *Determination of the diastolic pressure*

With the pressure continuing to fall slowly and uniformly, the sound increases to its maximum intensity and then decreases, at first gradually and later suddenly, and soon disappears. The point where the loud clear sounds change abruptly to the dull and muffled sounds should be taken as the diastolic pressure.

The American Committee recommend that if there is a difference between this point and the level at which the sounds disappear completely the latter reading should be regarded also as a measure of the diastolic pressure. This should then be recorded in the following form—Rt (or Lt) 140/80–70 or 140/40–0, or if these two levels are identical as 140/70–70. The British Committee disagree with this recommendation and think that except in aortic regurgitation it is nearly always possible to decide the point at which the change comes and that this is the only reading that should be recorded.

EXPLANATORY NOTES

The Committees feel that certain other considerations in addition to these specific recommendations should be taken into account, and for convenience they are numbered in the same way as the relevant recommendations.

1. *The instrument*

Frequent discussions have taken place as to relative merits of various types of blood pressure apparatus. The mercury manometer and the aneroid type of apparatus are both capable of correct readings if in good condition, and both may be inaccurate if they are not. This is sometimes neglected in reference to the mercury manometer, which should be tested at intervals in the following ways :

(*a*) The level of the mercury at rest should be at the zero mark. If any mercury has leaked out it must be replaced.

(*b*) If the small air vent at the top of the glass tubing becomes clogged there may be a lag which will give false readings.

(*c*) The blood pressure box must be on a level surface, since tilting of the manometer will lead to mistakes ; it should also be level with the observer's eye.

The aneroid type of instrument, if used, must be calibrated frequently against a mercurial manometer. The needle should stand at zero when the rubber tubing is deflated, and move immediately when inflation begins. A stop pin at the zero mark makes it difficult to check its accuracy.

In both types of instrument the valve must be competent. The entire system, including the rubber tubing and bag, must be free from leakage.

The rubber cuff must be at least 12 cm. wide ; it must be 23 cm. long and its covering must be of inextensible material and, if not of leather or made rigid with metal ribbing, should extend as a band 15 cm. wide for a distance of 60 cm. beyond the edge of the rubber cuff and then taper gradually to an apex during a further length of 30 cm. If bulging occurs the reading may not be accurate.

For children the rubber cuff may be narrower and the covering shorter.

New types of cuffs, using a zipper mechanism or rubber hooks on a ribbed extension the same width as the cuff, may prove to be more satisfactory than the long tapering cuff end.

2. *The patient*

The sitting position was selected by the American Committee because for practical purposes it simplified the taking of large numbers of blood pressure readings. The British Committee did not think there was any significant difference between the readings obtained in the sitting and lying positions.

Certain physical and psychological factors should be considered. Enquiry should be made as to the patient's activity just before the examination, as strenuous exercise may produce changes in the figures recorded. Blood pressure observations taken immediately after meals differ from those taken before

meals. There are physiological variations in the level of the blood pressure, so that for research purposes observations should be made with the same relationship to meals, sleep, exercise, and allied factors.

A rest period of from 10 to 15 minutes before taking blood pressure readings would eliminate or minimize certain of these factors. Tachycardia in itself sometimes causes a raised systolic pressure. Appreciation of the stress or anxiety through which the patient is passing is important to the examiner. Any appearance of concern on his part may unduly alarm the patient, thereby increasing the pressure. Apart from this, the first reading is often much too high because of the patient's nervousness.

3. *Application of the cuff*

Venous congestion must be avoided as far as possible ; there should be no constricting bands on the patient's arm and the pressure cuff should not be kept inflated longer than is necessary to take the reading ; it must be deflated completely before any further determinations are made. In obese subjects special care in the application of the cuff is necessary to prevent bulging. Deflation should be at the rate of about 3 mm. of mercury per second.

4. *The systolic blood pressure*

If the method of palpation is used before the auscultatory method as recommended, the unusual case with a silent gap will not be missed. In these cases after the first sounds have been heard there is an auscultatory gap below which the sounds reappear. This silent gap is not very uncommon in cases of aortic disease and hypertension

8. *Cardiac arrhythmias and aortic valvular disease*

The determination of blood pressure in these conditions is more difficult and the following recommendations are made :—

(*a*) Where there are extrasystoles the higher pressure of the beat that follows should be ignored.

(*b*) In auricular fibrillation only approximate blood pressure readings can be obtained ; the systolic value should be taken at the point where the majority of beats appear, and the diastolic (if at all) at the point where they become dull and muffled. The American Committee suggest that the average of a series of such readings should be noted as the systolic and diastolic pressures.

(*c*) Alternation in the strength of the beats (Pulsus alternans) must be looked for carefully. It must be distinguished from the alternating values produced by regular alternate extrasystoles (Pulsus bigeminus).

(*d*) In aortic stenosis with a slow rising or anacrotic type of pulse, auscultation may give a false systolic reading and palpation may be more accurate ; often a satisfactory diastolic reading cannot be obtained.

(*e*) In aortic regurgitation with a collapsing pulse the diastolic and point is marked by a less obvious change in the quality of the sounds, which may be difficult to appreciate.

9. *General*

In speaking of the changes which the sounds undergo, the term *points* is suggested for use instead of the commonly used term *phase*, since the latter implies a period of time, whereas the *points* are in fact the precise moments at which one phase changes into the next.

The use of a single figure for a pressure that varies so rapidly cannot be accurate to within from 5 to 10 mm. of mercury. For special accuracy several determinations should be made and the highest and lowest should be recorded.

If the pulse feels different on the two sides the blood pressure should be taken in both arms.

In the presence of unexplained high pressure in the arm it should be taken in the leg also, so that coarctation of the aorta may be detected.

A special cuff is necessary to record the blood pressure easily and accurately in the leg. The rubber bag should be 15 cm. wide and its covering should be 17 cm. wide and 30 cm. longer than in the case of the armlet. The patient should be in the prone position with the leg extended and the sounds should be auscultated over the popliteal artery.

In detailed researches on blood pressure the use of a basal pressure might be considered, after preparation similar to that used for basal metabolism. It should be determined 10–12 hours after the last meal of the previous night, and after resting half an hour in a warmed room. Difficulties in the use of this procedure in practice are obvious, and observations suggest that after 15 minutes the pressure has generally fallen to a basal level.

A defect of hearing in the examiner may call for the use of a stethoscope with some form of amplifier.

It is hoped that a critical attitude towards this subject on the part of physicians generally will result from the efforts of these Committees, so that every precaution will be taken to obtain conscientious and unbiased records through the use of the standard technique suggested here. These recommendations are not intended to discourage other methods of observation when indicated in special situations.

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